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X-RAY DIFFRACTION STUDIES ON NERVE

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FROM analysis by means of polarized light it has long been known that nerves possess a high degree of molecular organization. The axis cylinder is positively birefringent due to the presence of anisotropic material, the optic axis of which lies parallel to the long axis of the fiber. The myelin sheath is constructed of lipoid fluid crystals with optic axes perpendicular to the direction of the fiber and radially oriented (Schmidt, 18). The positive birefringence of the axis cylinder is due presumably to the protein neurofibrils which, though visible in fixed and stained preparations, have never been demonstrated in living medullated axons under physiological conditions (Peterfi, 16). In view of the success with which the x-ray diffraction method for fine-structure analysis has been applied to certain other fibrous animal tissues such as hair, chitin, connective tissue, etc., it is desirable that full use be made of this tool in the case of nerve, particularly since modern research on nerve energetics reveals that impulse propagation takes place with but extremely small initial energy liberation. Hill (11) has shown, for example, that the heat production immediately accompanying the propagated disturbance in frog nerve at room temperature is so low as to be near the limit of measurement. It seems obvious that any mechanism capable of propagating an electric potential wave at a velocity of 30 meters per second so efficiently must owe its properties in no small measure to the molecular organization which acts as the physical substratum for the impulse propagation.

Considerable advance has already been made in this direction (Herzog and Janke, 10, Handovsky and Thiessen, 8, Handovsky, 9, and Boehm, 5). Boehm, whose work is the most extensive thus far, obtained the following results: The pattern for fresh nerve consists of a ring with meridianal sickles at 4.8 Å. and equatorial points at 17 Å. The latter points decrease with drying to 11 Å. By a comparative study of nerves with varying proportions and degrees of development of the myelin sheath, axis cylinder, and connective tissue, he concluded that the 4.8 Å. ring is produced by the radial fluid crystals of the myelin sheath, while the 17 Å. equatorial points are produced by connective tissue. Neurofibrils, according to him, either do not exist or have a side spacing greater than 25 Å. (limit of

[1] We are greatly indebted for excellent assistance in producing the x-ray patterns with greatly improved technic to Dr. J. N. Mrgudich, N. C. Schieltz, and E. A. Parker, of the X-ray Laboratories, Department of Chemistry, University of Illinois, and for aid in the making of electrical tests to Mr. Otto Schmitt, of the Physics Department, Washington University.

his apparatus); the axis cylinder is a tube filled with a structureless, rather viscous gel.

Schmitt and Wade (19, 21, 22) found that nerve shows striking thermal shortening and reacts to solvating and desolvating agents in a manner similar to that of other fibrous tissues such as tendon. These effects were thought to be due, at least partially, to the axis cylinder. In view of the recent work on the significance of thermal shortening and swelling of fibrous tissues (see particularly Meyer, 15, and Kuentzel and Prakke, 13), this indicated a certain degree of orientation in the fresh axis cylinder. We entered upon the present work not only with the hope of obtaining further information regarding the structure of the axis cylinder but also because of the feeling that by improved technic more details of the fine structure of nerve might be acquired by the diffraction method, the number of spacings reported by Boehm and others being disappointingly few.

METHODS AND APPARATUS

Since the spacings in nerve are large it is desirable to use large wave lengths. In this work the Kα radiation of copper was used as obtained from a Philips Metalix tube operated at 35–40 K.V. and 20–25 milliamperes. The film was held in a flat holder, the distance from specimen to film varying with the experiment; in most cases the distance was 3 centimeters. The diameter of the pinholes depended also upon the type of experiment being performed. At distances of 3 cm. both front and back pinholes were 0.6 mm. in diameter. For work on large spacings (specimen-to-film distances up to 20 cm.) the pinholes were reduced to a diameter of 0.2 millimeter. The lead beads were always as small as possible and were very carefully centered before each exposure. These precautions with bead and pinhole size are of great importance. Boehm, using 2 mm. pinholes, failed to observe the large equatorial points at 40–45 Å. and thus was led to an incorrect interpretation of certain features of the remainder of the pattern.

Dried preparations were simply laid over the pinhole and held attached by means of plasticene. For short exposures the patterns of fresh nerves were obtained in a similar manner except that the nerve was kept moist by frequent spraying with Ringer solution from an atomizer. At large specimen-to-film distances when the time of exposure was prolonged the nerve was suspended on a thin glass stirrup and kept in a moist chamber of very small volume to prevent drying. The stirrup was connected to a mechanism by means of which the nerve could be moved in front of the pinhole so as to change the radiated point frequently. The moist chamber was provided with glass windows approximately 5μ in thickness.

Boehm, as a result of his work on muscle (4), which indicated that the radiation has a decidedly toxic effect, took the precaution of changing the radiated region of the nerve during the exposure. This is obviously an important point, and we determined its significance at the outset of our work. If the radiation produces artificial changes, the patterns resulting may likewise be patterns of the artifacts. To test this point under the worst possible conditions we simply laid a fresh nerve, still connected to its muscle, over the pinhole, keeping the muscle and unexposed portions of the nerve moist with cotton soaked in Ringer solution and moistening the exposed portion of the nerve with an atomizer frequently. Using the threshold method it was found that radiating sufficiently long to obtain a good pattern (10 min.), without changing the radiated spot, had no effect whatever on the irritability of the nerve as measured by the threshold method. This method, however, tests the condition of the most irritable fibers only. To obtain information on the condition of the nerve as a whole, action potentials were measured with the cathode-ray oscillograph before and after radiation. The results show that as long as the nerve was not allowed to dry, the radiation

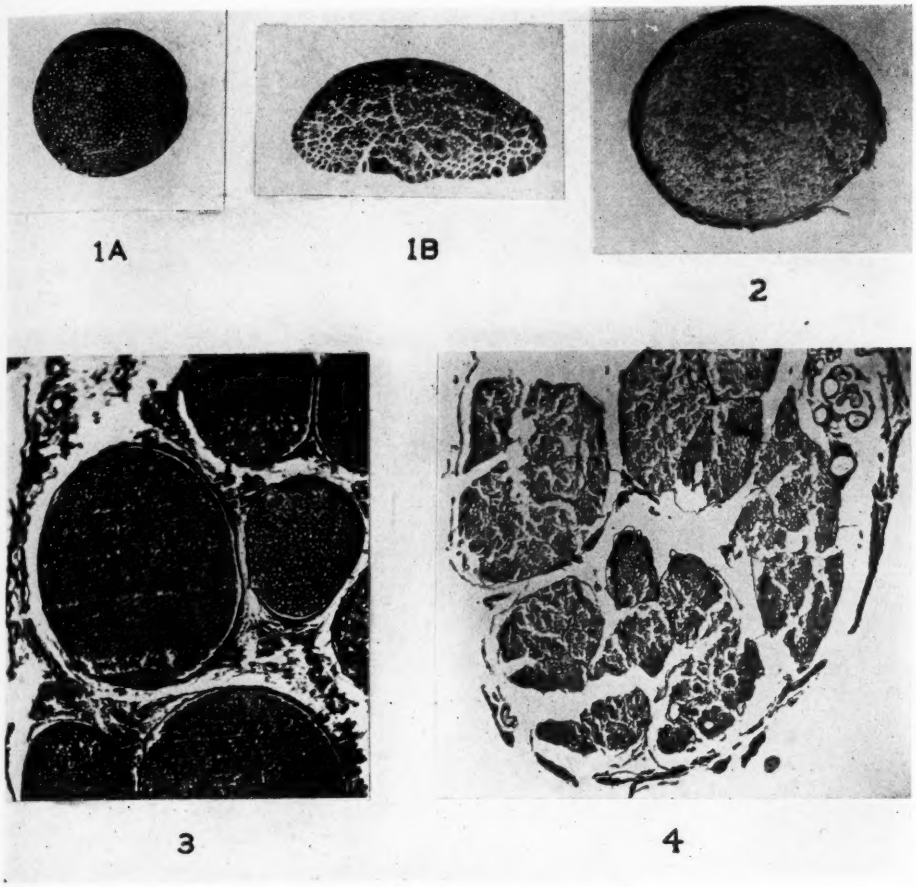

Plate 1. Photomicrographs of nerve tissue prepared as described in text. Magnification: Figs. 1 to 3, 48×; Fig. 4, 62×. Fig. 1-*A*. Bull frog motor root. Fig. 1-*B*. Cat motor root. Fig. 2. Branch of bull frog sciatic. Fig. 3. Cat sciatic. Fig. 4. Lobster leg nerve.

produced no decrease in the action potential, even when the usual exposure time was trebled; indeed, in several instances the action potential was slightly increased by the radiation. Nerves tested in this manner were the sciatic of the frog and motor and sensory roots of the bull frog and cat.

Selection of Material.—Boehm's choice of material with which to make a comparative study of the rôle of axis cylinder, myelin sheath, and connective tissue was incomplete. The structures to which physiological interest attaches are the myelin sheath and axis cylinder, and nerve types should have been selected so that at least one representative type contained these two structures well developed, but no connective tissue. To provide such types we chose the following tissues: corpus callosum, motor roots, sensory roots, sciatic nerve. The corpus callosum may be regarded as the simplest type of medullated material, containing not only no connective tissue, with the exception of glia cells, the chemical nature of which is uncertain, but also no sheaths of Henle or Schwann; moreover, the axis cylinder is not interrupted by nodes of Ranvier. The motor roots of the cat are practically entirely free of

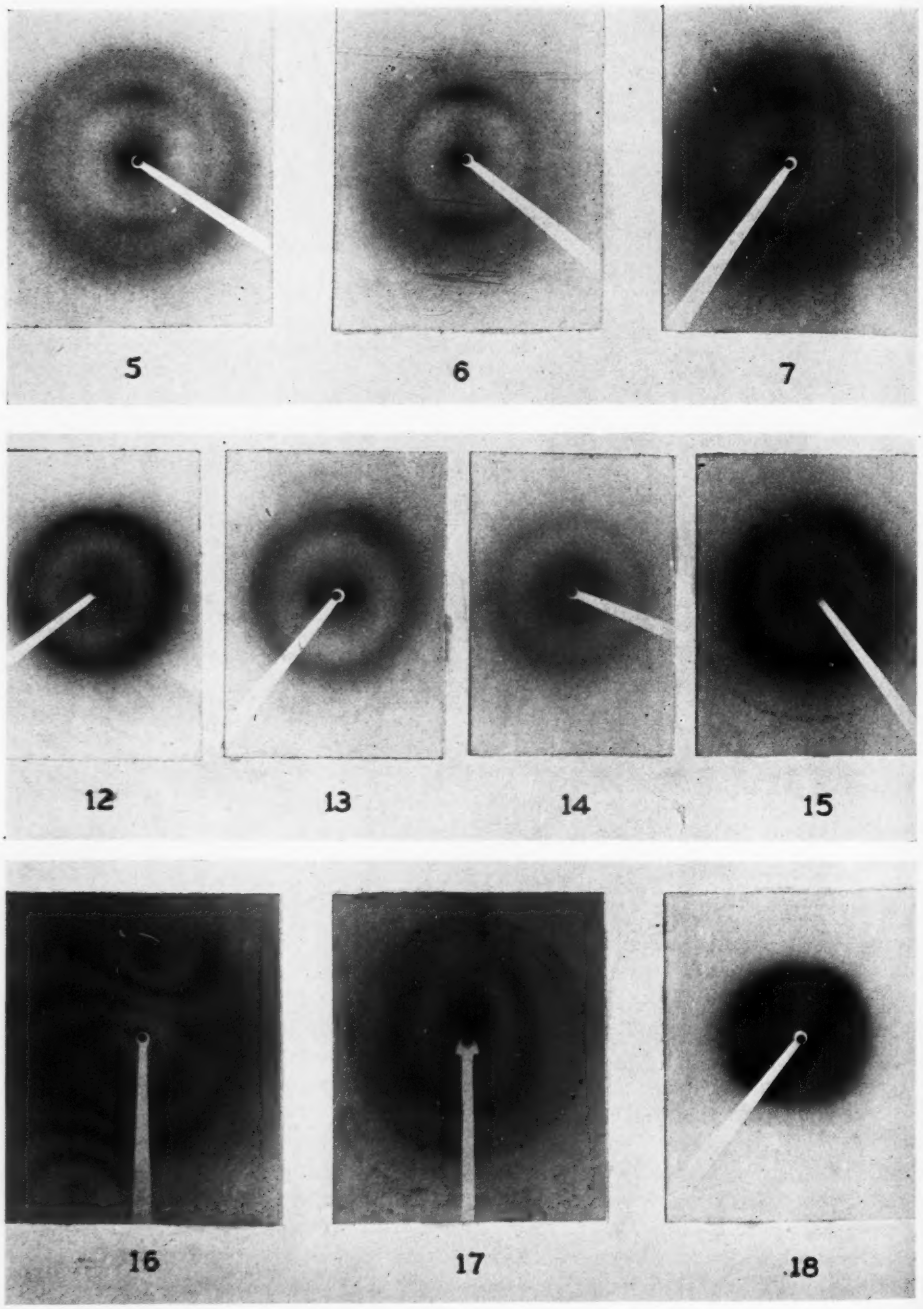

Plate 2. Diffraction patterns of nerves under various conditions. Distance from specimen to film (D) = 3.0 cm. All patterns are reproduced without alteration in size. Fiber axis is vertical in each case. Fig. 5. Fresh frog sciatic. Fig. 6. Fresh cat motor root. Fig. 7. Fresh cat corpus callosum. Fig. 12. Cat corpus callosum dried in desiccator. Fig. 13. Cat sciatic dehydrated in alcohol under tension. Fig. 14. Bull frog motor root dehydrated in alcohol under tension. Fig. 15. Frog sciatic dehydrated by the Scott freezing drying technic. Fig. 16. Lobster claw nerve fresh. Fig. 17. Lobster claw nerve dried in desiccator. Fig. 18. Lobster claw nerve dehydrated in alcohol under tension.

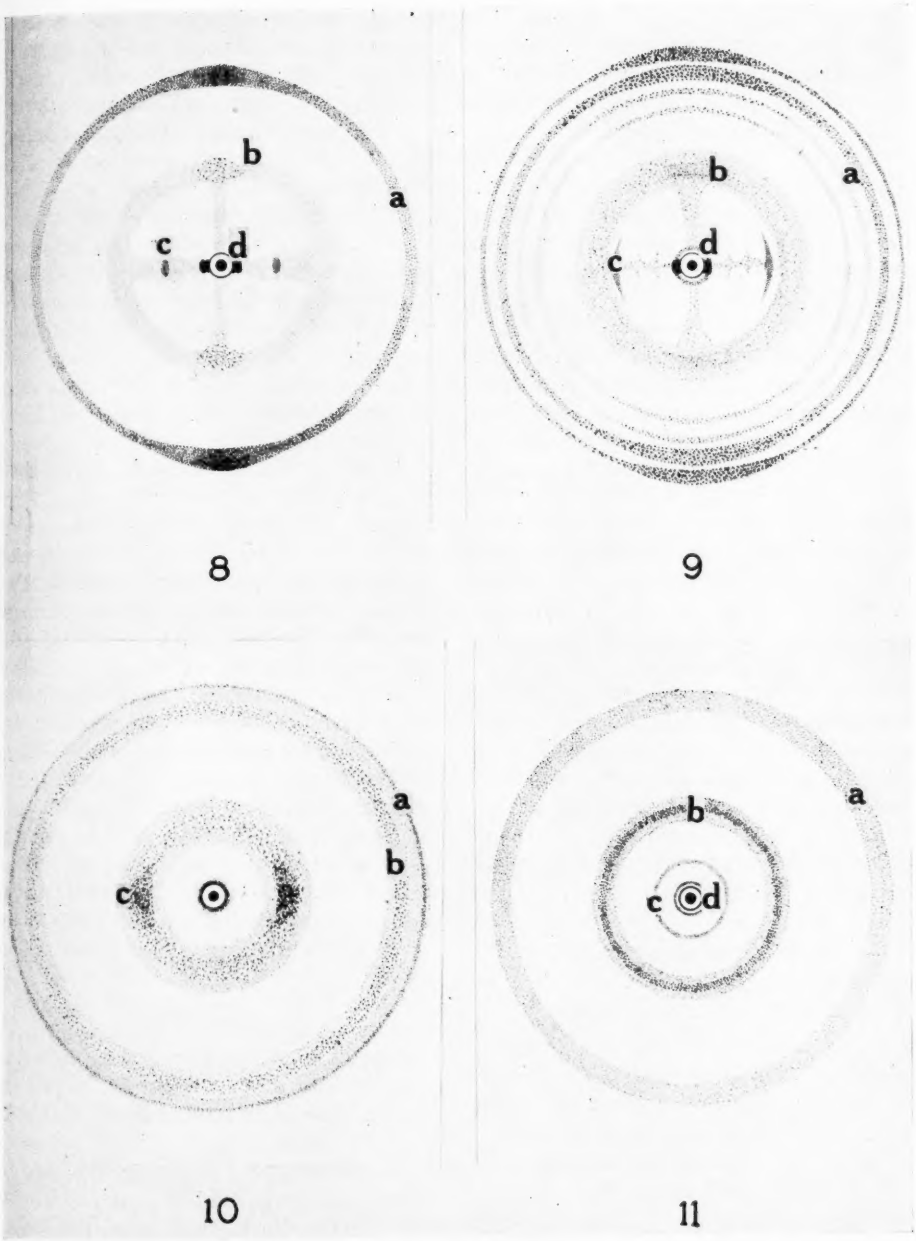

Plate 3. Fig. 8. Fresh medullated nerve. *a*, 4.7 Å. meridianally sickled rings; *b*, 9.4 Å. meridianal spot; *c*, 15.5 Å. equatorial point; *d*, large-spacing equatorial points. Fig. 9. Stretched and dried medullated nerve. *a*, meridianally accentuated rings at 4.20, 4.67, 5.20, and 5.8 Å.; *b*, 10 Å. meridianally accentuated ring; *c*, 11.5 Å. equatorial point; *d*, large-spacing equatorially accentuated rings Fig. 10. Lobster or crab claw or leg nerves dehydrated in alcohol under tension. *a*, 4.2 Å. ring; *b*, 4.8 Å. ring; *c*, 11.5 Å. equatorial sickle. Fig. 11. Artificial fiber made by spinning nucleoprotein solutions (neutral-soluble extract or neurostromin from dried lobster nerves or cow spinal cord) into alcoholic acetic acid. *a*, 4.8 Å. ring; *b*, 9.1–11.5 Å. ring; *c*, 23 Å. ring; *d*, 48 Å. ring.

connective tissue. In the frog there is a thin outer membrane enveloping the roots, and interfibrillary connective tissue is very scanty. The Schwann sheath is present and the axis cylinder is interrupted by nodes of Ranvier. The sensory roots resemble the motor roots except that there is slightly more interfibrillary connective tissue, the amount being small as compared with peripheral nerve. In the sciatic, the connective tissue is said to constitute over half the bulk of the nerve. To check the statements found in the literature regarding the structure of these nerves we made a histological examination of the various types under discussion with methods designed to differentiate connective tissue.[2] Immediately after obtaining a diffraction pattern each nerve was plunged into formol-Zenker solution and after embedding in paraffin, sectioned and stained. Figures 1 to 3 show the great difference in amount of the connective tissue in spinal roots and sciatics. The present series provides an excellent opportunity to study the possible orientation, not only in myelin sheath, axis cylinder, and interfibrillary connective tissue, but also in the Schwann sheath. The leg and claw nerves of the lobster and crab were used as examples of non-medullated types (see Fig. 4).

EXPERIMENTAL RESULTS

The nerve patterns about to be described were obtained with 0.6 mm. pinholes and with the film 3 cm. from the specimen. Details of the larger spacings obtained at long specimen-to-film distances will be given in a later section.

Fresh Nerve

1. *Medullated Nerve.*—It is significant that the patterns obtained from each type of medullated nerve were essentially similar. Included in the series were cat corpus callosum, motor and sensory roots, spinal cord, sciatic and vagus, bull frog spinal cord, motor and sensory roots and sciatic, and green frog sciatic. Typical patterns are reproduced in Figures 5 to 7.

Aside from the water halo at 3.3 Å., fresh medullated nerve patterns show a ring with meridianal sickles at 4.6–4.8 Å., together with equatorial points at about 15.5 and 40–45 Å. The equatorial spacings tend to elongate into sickles and under certain conditions even into rings. They were seen as clear-cut points best in corpus callosum and spinal roots. There is usually also a very diffuse ring or halo at from 7.5 to 10.5 Å. While this halo may have several origins it is possible that the proteins of nerve may be responsible for the larger spacing. In a number of favorable photographs of corpus callosum and spinal roots it was possible to distinguish a meridianal spacing at about 9.4 Å. The location of the various spots and rings are indicated on the idealized diagram, Figure 8.

2. *Non-medullated Nerve.*—The pattern obtained from fresh leg or claw nerves of the lobster or crab consists merely of two diffuse water halos, one at 3.3 Å. and the other extending between the approximate limits 5–16 Å. The latter halo doubtless corresponds to that described by Thibaud and Trillat (26) as resulting from the continuous radiation of the x-ray source when thick scattering materials are employed.

Dried Nerve

Drying was usually accomplished by hanging the freshly dissected nerve in a desiccator with a small weight attached to prevent curling.

1. *Medullated Nerve.*—Perhaps the principal change in the patterns of fresh nerve with drying concerns the 15.5 Å. equatorial points or sickles. With simple drying, these points disappear or become extremely faint. Coincident with this fading, a new spacing, somewhat equatorially accentuated but appearing usually as a ring, can be seen at approximately 11.5 Å. (Fig. 12). The 40–45 Å. equatorial

[2] We are much indebted to Dr. James O'Leary for advice and assistance with the neurohistological technic.

points apparently become elongated into sickles, but this spacing is so close to the central spot at 3 cm. distance that its behavior with drying must be studied at greater distances. The 4.7 Å. ring becomes very considerably broader and there is a tendency toward inhomogeneity (this effect is accentuated in stretched nerves and will be described later).

It is obvious, both from the 4.7 and 40–45 Å. spacings, that drying produced considerable disorientation instead of sharpening the picture as might have been expected. It is a well known fact of cytological technic that if dehydration is produced too rapidly, distortion of the orientation of fine fibrils may result. We, therefore, tried a method of very slow dehydration in which the fresh nerves, held stretched out by a 5-gram weight, were transferred to 35 per cent alcohol and thence by very slowly increasing alcohol concentrations eventually into absolute alcohol (the entire process usually lasted about four days). The nerves were then allowed to remain in absolute alcohol for a period of weeks with occasional renewal of the solution. Bull frog motor and sensory roots and green frog sciatics so treated yielded patterns in which equatorial sickles at 11–12 Å. were prominent, whereas the 4.7 and 40–45 Å. spacings were fainter and entirely unoriented. In cat sciatic and cat vagus nerves, aside from the 11–12 Å. sickles, thin, clear, meridianal sickles appeared at about 2.7 Å. In Figures 13 and 14 are given typical patterns of alcohol-dried medullated nerves.

We also tried the effect of the liquid air freezing-drying technic[3] which is said to dehydrate tissues with a minimum of distortion, but the results indicated as much if not more disorientation than that produced by plain drying in the desiccator (Fig. 15).

2. *Non-medullated Nerves.*—It is interesting to note the changes in the diffraction pattern which occur as the claw or leg nerves of the lobster are slowly dried in a desiccator. The first change is the fading and disappearance of the inner water ring. With further drying, before the water ring at 3.3 Å. disappears, a rather faint ring appears in the neighborhood of 9–11 Å. After complete drying, along with numerous salt rings, a new ring at approximately 4.7 Å. appears. This ring, which is quite broad, appeared in several instances to be resolved into separate rings at about 4.2 and 4.8 Å.

Even when stretched and dried, lobster nerve shows little tendency toward fibering. In a few instances the 11.5 Å. ring appeared to be intensified at the equator, but the orientation must have been very weak. However, claw nerves slowly dehydrated in alcohol under tension by the process described above showed sharply sickled equatorial spacings between 11 and 13 Å. The ring at 4.7 Å. is very much fainter in these nerves than in those dried in a desiccator and faint, thin, meridianal sickles appear at 2.8 Å. The large equatorial spacing at 45 Å. was not observed in lobster nerves, although in a few instances its presence has been suspected. Figures 16 to 18 show the various types of lobster nerve patterns, while Figure 10 diagrams the alcohol-dried lobster nerve pattern.

Interpretation of Nerve Patterns.—These patterns of fresh and dried medullated and non-medullated nerves were previously interpreted as follows (20). In the first place it was pointed out that the 15.5 Å. equatorial points of fresh medullated nerves are not due exclusively to connective tissue, as claimed by Boehm. If this were true, then, in our series, fresh sciatics should show the spacing best and spinal roots and corpus callosum not at all. Just the opposite is the case. The clearest and best oriented examples of this spacing were obtained with fresh corpus callosum and spinal roots. The remote possibility that the thin epineural sheath of spinal roots, which does show

[3] The frog sciatics and spinal cords were prepared according to this technic by Dr. G. H. Scott, to whom we wish to express our appreciation.

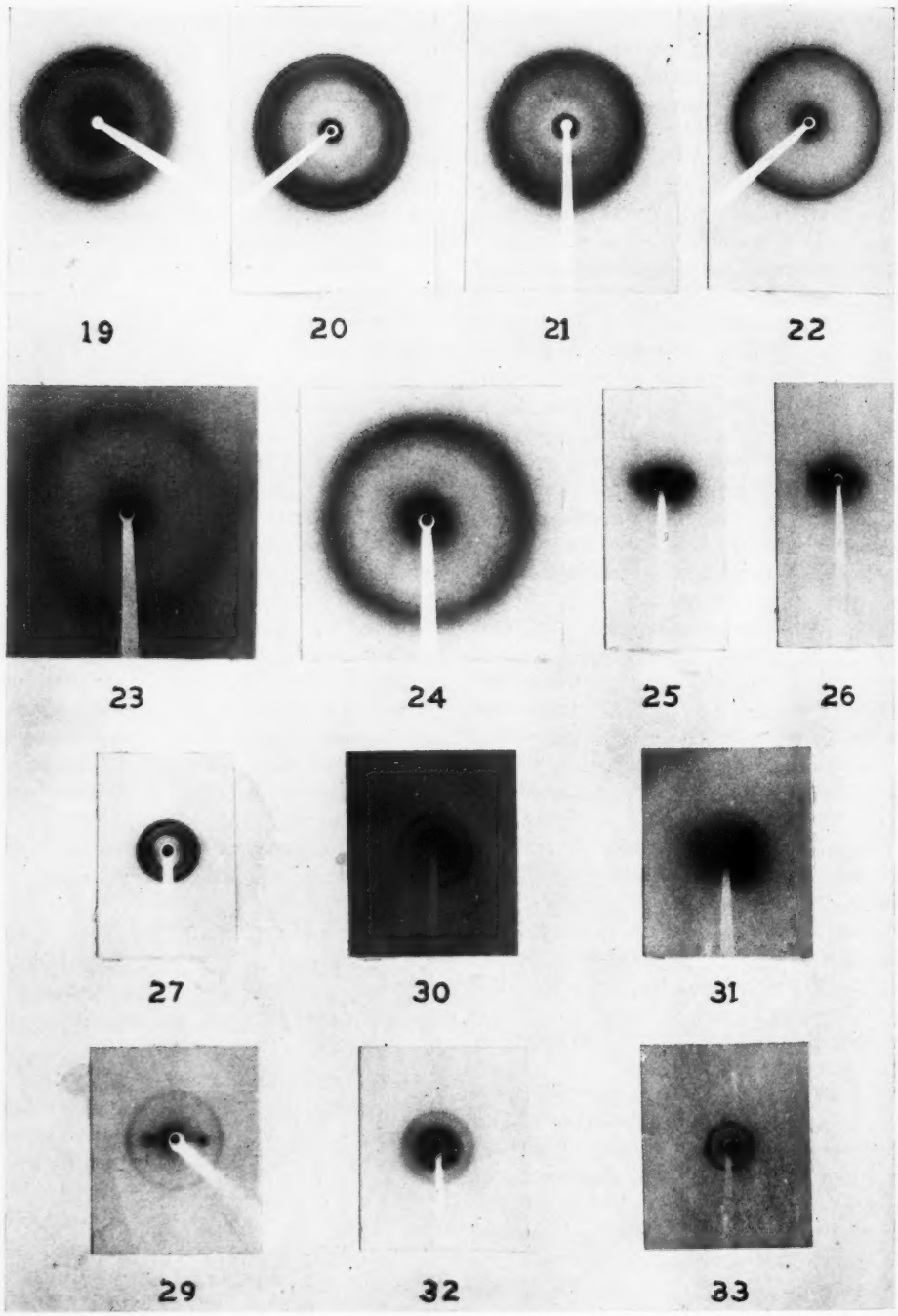

Plate 4.

(19) Bull frog motor root stretched 34 per cent while in fresh condition and dried in desiccator while stretched. D = 3.0 cm. (20) Lipoids from benzene extract of dried cow spinal cord. D = 3.0 cm. (21) Lecithin. D = 3.0 cm. (22) Artificial fiber made by spinning a benzene extract of dried cow spinal cord into acetone. D = 3.0 cm. (23) Benzene extract of dried cow spinal cord rubbed up with water and mounted on loop before pinhole. D = 4.4 cm. (24) Same as

positive birefringence, or the Schwann sheath may be responsible for the spacing is ruled out by the clearness of the points drying would indicate intramicellar swelling. Since connective tissue was ruled out as the source of the 15.5 Å. points,

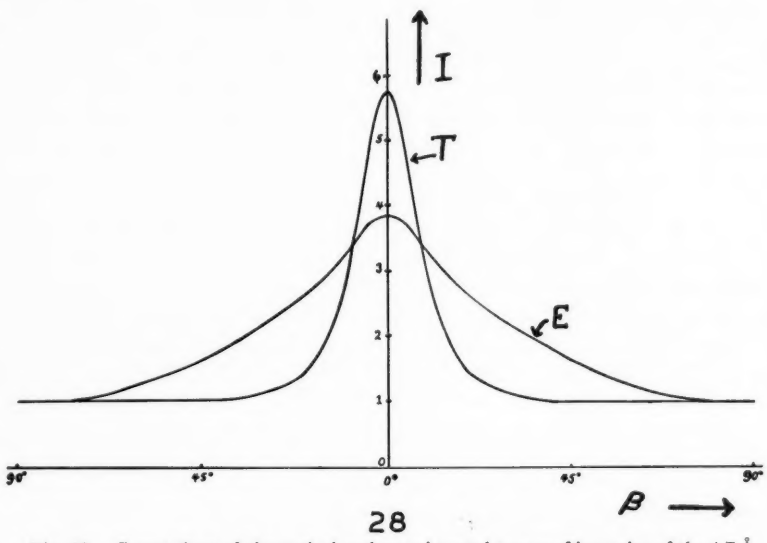

Fig. 28. Comparison of theoretical and experimental curves of intensity of the 4.7 Å. ring. *I* represents intensities relative to that on the equator; β represents the angle of departure from the meridian; *T* is the theoretical curve; *E* is the curve obtained from densitometer readings of a typical pattern of fresh medullated nerve. For further details see text.

in corpus callosum, which is devoid of such sheaths.

It is impossible to say that connective tissue in such nerves as the sciatic does not contribute to the spacing at 15–17 Å. typical of medullated nerve. That this contribution must be small, however, is indicated by the fact that even fresh muscle, which is rich in connective tissue, yields no such characteristic spacing (Boehm, 4).

The analogy with collagen fibrils, pointed out by Boehm, is striking. In nerves, just as in collagen, drying causes the disappearance of the 15–17 Å. spacing and the appearance of a more or less oriented equatorial spacing at 11–13 Å. On the assumption that protein fibrils are the cause of both spacings, the decrease with the tentative view was taken that this spacing is produced by axis cylinder proteins. This view was strengthened by the fact that while, to be sure, no points at 15.5 Å. were obtained in fresh lobster nerve, very clear equatorial points and sickles at 11–13 Å. were gotten from lobster and crab nerve slowly dehydrated under tension in alcohol. Crab claw nerve is said by Boehm to be practically 100 per cent axis cylinder material. That the 4.7 Å. ring with meridianal sickles may be another protein spacing, presumably representing periodicities along the lengths of much folded chains, was suggested largely because this spacing was found also in dried lobster and crab nerve; the latter, according to Boehm, contains only negligible amounts of lipoid.

Figure 23 except that lipoids had been allowed to dry for three hours. D = 4.44 cm. (25) Fresh bull frog motor root mounted on stirrup in moist chamber. D = 10.95 cm. (26) Fresh frog sciatic mounted on stirrup in moist chamber. D = 11.11 cm. (27) Lipoids from benzene extract of dried cow spinal cord. D = 12.80 cm. (29) Bull frog motor root dried in desiccator. D = 20.80 cm. (30) Mixture of cholesterol and lecithin rubbed up with water and smeared on stirrup in moist chamber; further details in text. D = 11.10 cm. (31) Same as Figure 30 except that stirrup had been removed from moist chamber and lipoids dried for seven hours. D = 12.30 cm. (32) Lecithin rubbed up with water, mounted on stirrup and placed in moist chamber. D = 11.10 cm. (33) Same as Figure 32 except that stirrup had been removed from moist chamber and lecithin allowed to dry for seven hours. D = 11.19 cm.

It had been found (22) that nerve when treated with certain solvating reagents such as thiocyanate shows a type of supercontracture in certain respects similar to that of keratin. Under these conditions both medullated and non-medullated nerves shorten from 60 to 70 per cent and show perfectly reversible elasticity when stretched to and somewhat beyond the original length. Indeed, even normal untreated nerves may be stretched without rupture as much as from 40 to 50 per cent, although this stretching is not reversible as in the case of supercontracture. On the assumption that the nerve pattern was due largely to oriented protein chains it became desirable to determine whether stretching might produce a new form comparable to the α-β shift found by Astbury for keratin (1) and more recently also for muscle (2). We, therefore, obtained patterns from nerves, particularly spinal roots, which had been stretched and dried while stretched. These photographs revealed no apparent change on the equator which might be interpreted as indicating an α-β shift. They did, however, reveal a very interesting separation of the 4.7 Å. ring into a series of rings with meridianal accentuation, the principal ones having spacings of approximately 4.2, 4.7, 5.2 and 5.7–5.9 Å. (Figs. 19 and 9). At this time also, in the course of an investigation on the chemical composition of unmedullated nerve it was found (3) that the lipoid content of lobster nerves, far from being negligible in amount, may be as high as 25 per cent of that of the white substance of the brain. This, together with the difficulty of interpreting the separation of the 4.7 Å. ring into several rings with stretching and drying, upon the basis of proteins reopened the possibility that this ring may be due to myelin.

Diffraction Patterns from Extracted Nerve Lipoids.—To obtain more decisive evidence of the origin of the various parts of the nerve pattern, the lipoid and protein components were separated by a process of fractionation and the patterns of each constituent studied separately. Lipoid fractions were obtained by extraction of dried cow spinal cord with a mixture of 95 per cent benzol and 5 per cent alcohol. Such extracts were evaporated and the dried solid placed in loops before the pinhole (Fig. 20). The protein extraction will be described later.

These photographs (Figs. 20 to 22) revealed at once that the 4.7 Å. ring is due to the lipoids of the myelin sheath. Indeed, as will be shown, with the exception of the orientation effect,[4] the lipoids gave patterns which almost completely reproduced those of fresh medullated nerve including the 40–45 Å. spacing.

Since dried extracted lipoids gave patterns similar to those of dried medullated nerve, we next attempted to identify individual components responsible for the patterns of each. For this purpose it would have been desirable to obtain patterns from lecithin, cholesterol, cephalin, sphingomyelin, kerasin, phrenosin, nervon, and hydroxynervon, as the principal components of the myelin sheath. Of these we have so far tried only lecithin, as an example of the phosphatids, and cholesterol, to which the strong birefringence of the myelin is in great part due (see Göthlin, 7). Boehm believed the 4.8 Å. ring in fresh nerve due particularly to mixtures of cephalin and cerebrosides. These and other members of the above-named group will be investigated in the near future.

Powder crystal photographs of cholesterol revealed the spacings shown in Table I. Lecithin was obtained according to the method of Levene and Rolf (14). Although the sample used was somewhat darker in appearance than when freshly prepared, the degree of saturation was doubtless low. The material was rubbed into a loop and placed before the pinhole for radiation. The chief spacings found for lecithin are also given in Table I, the pattern and reproduction in Figure 21. It will

[4] In several of these smear preparations the patterns showed decided orientation, due presumably to the momentary stroking necessary in rubbing the material into the loop or stirrup. In such cases the same mutual directions of accentuation of the rings were observed with the lipoids as in nerve patterns.

be seen that the rings, observed in dried and stretched medullated nerves, at 4.20, 4.67, 5.20 and 5.7–5.9 Å. appear also in these lipoids, the 4.20 and 4.67 Å.[5] spacings apparently belonging to phosphatid and the 5.20 and 5.8 Å. spacings to cholesterol. Furthermore, extraction of the lipoids with acetone results in material for which the 5.2 and 5.8 rings are considerably weaker (Fig. 22). It is not implied that other nerve lipoids may not contribute to the pattern beside lecithin and cholesterol; it is very probable that they might, since the region from 4 to 6 Å. might well correspond to a dimension of the unit cell of any of them.

Since individual components of the myelin sheath (phosphatid and cholesterol) can be identified from the series of rings into which the 4.7 Å. ring of fresh nerve breaks up upon drying, we next attempted to reproduce the 4.7 Å. ring itself from wet lipoids. For this purpose the dried solid obtained by evaporation of the benzene extract of cow spinal cord was rubbed up with water and placed on the stirrup in the moist chamber before the pinhole. The patterns contained rings at 4.6 and 15.7 Å., both being spacings observed in fresh medullated nerve. The wet lipoids were then removed from the moist chamber and allowed to dry for three or four hours and another photograph made for the purpose of comparing the wet and dry pictures from one and the same preparation. The results are shown in Table I and Figures 23 and 24. Of significance in these patterns is the fact that not only do the extracted lipoids reproduce the behavior of drying medullated nerve with respect to the 4.6–4.8 Å. ring but also with respect to the 15.5 Å. ring. The latter spacing, which is prominent in the pattern of wet lipoids, greatly fades and almost disappears upon drying. Similar results were obtained also with lecithin and with a cholesterol-lecithin mixture.

[5] The 4.67 Å. spacing is undoubtedly complex, as pictures taken at large specimen-to-film distances with nerve lipoids have indicated. However, the greater proportion of phospholipids present in nerve would make it seem likely that scattering in this position is in greater part related to the 4.65 lecithin (or phospholipid) spacing.

This discovery of the presence of a spacing at approximately 15.5 Å. in lipoids and of the fact that this spacing tends to fade with drying necessitated a radical change in our views of the rôle of axis cylinder proteins in nerve patterns. Up to this time we had assumed, in analogy with the case of collagen, that the 11.5 Å. equatorial points of dried nerve corresponded to the 15.5 Å. points of fresh nerve, the decrease in spacing being caused by intramicellar desolvation. The possibility now presented itself that there may be no connection between the 15.5 Å. and 11.5 Å. spacings, since the behavior, in nerve, of the former with drying can be reproduced with lipoids free of protein. Such an eventuality would remove our diffraction evidence for the existence of oriented protein chains in the axis cylinder of fresh nerve, hence the interpretation of this spacing became one of our chief concerns.

If this spacing is due to lipoid, it almost certainly must represent a spacing in the *c* direction because of its orientation and because the lipoids in the myelin sheath are known to be incorporated in fluid crystals whose optic axes lie radially. However, Thiessen and Spychalski (27) had shown that lipoids such as the oleates associate end-to-end in pairs giving *c* spacings of the order of 42–45 Å. We had in fact come to regard our 40–45 Å. equatorial points as representing such a spacing in the fluid crystals of the myelin sheath, since similar spacings were observed in extracted lipoids and in lecithin smears. The clue which led to the solution of the problem was the fact that several of our 3-cm. photographs of fresh motor roots in which the bead happened to be slightly off-center showed the 40–45 Å. spacing undoubtedly complex, with an outer difficultly measurable point lying roughly at 35 Å. This suggested the possibility that both the 15.5 and the 35 Å. points might be higher orders of a larger fundamental spacing which was indicated in our pictures but which was too close to the primary beam for measurement.

Large Spacing Photographs.—To obtain greater detail with respect to the large

spacings, photographs were made with very small pinholes (0.2, 0.2, 0.2 mm.), well centered small beads, and with distances of 10–20 cm. from specimen to film. The exposure time was considerably greater for these photographs, although very good patterns were obtained from lipoids, for example, in one-hour periods. The results were surprising and highly significant. Fresh bull frog motor root or green frog sciatic showed rings with very clear equatorial accentuation at 85.5, 56.8, 42.7, 34.2, and 15.5 Å. (Figs. 25 and 26). The first four clearly represent the second, third, fourth, and fifth orders of a unit spacing of 171 Å. On this basis, the 15.5 Å. represents the eleventh order. Why the eleventh order should show up when all the intervening orders are either absent or too faint to be measured is not clear, although the intensities are such that the 15.5 spacing might very easily represent such a high order.

The discovery of such large spacings previously unsuspected for nerve or other animal tissues caused us to reinvestigate all of our material with the object of revealing large spacings. The results are included in Table I, which is a composite table without reference to the specimen-to-film distance at which each spacing was obtained.

Considering first the light which these long-distance photographs throw on the structure of medullated nerve, one can say with considerable certainty that the 15.5–16 Å. equatorial points and sickles of fresh nerve are produced by the lipoid fluid crystals of the myelin sheath. The entire picture, therefore, of fresh medullated nerve, would be due to the myelin sheath. This interpretation requires the assumption that the *c* axes of the myelin sheath fluid crystals are surprisingly well oriented. Is this assumption justified? To answer

TABLE I. —COMPOSITE TABLE OF SPACINGS FOUND IN NERVES

Fresh Medullated Nerve	Alcohol-dried Medullated Nerve	Alcohol-dried Non-medullated Nerve	Stretched Dried Medullated Nerve	Dried Nerve Lipoids	Wet Nerve Lipoids
	2.73 Å. fMS	2.81 Å. fMS	2.77 Å. fMS	3.36 fR	
	4.2 mMR	4.2 mR	4.20 sMR	4.17 sR	
4.6–4.8# sMSR	4.8* mMR	4.8* mR	4.67* mMR	4.66* mR	4.6 Å. sR
			5.20 mMR	5.20 sR	
			5.8 fMR	5.8 mR	
				6.4 fR	
9.4 ffMS	10 ffMR		10 fMR	7.3–10.4′ fR	
	11.5 mES	(11–13)# mES	11.5 mES		
15.5 mfES				16 ffR	15.7 mR
				23 ffR	
34.2 mES				33.3 fR	
42.7 ssES	See Stretched-dried Nerve		43 sER	44.5 ssR	Too Dense for Measurement
56.8 mES				67.5 ssR	
85.5 ssES			71 sES		
			140 ffES		

Explanation: ff, f, mf, m, s, ss indicate degrees of increasing intensity from very faint to very strong.
M and E indicate meridianal (along fiber) and equatorial (transverse) intensifications, respectively.
S is employed to indicate strong intensification in a specified direction; R represents a ring.
′ Figures given are limits of diffuse rings.

this question a calculation was made[6] of the intensity to be expected at any point along the 4.6–4.8 Å. ring of fresh nerve on the assumption that the *c* direction (planes parallel to which are considered to be forming the ring) of the myelin sheath crystals is always directed radially and perpendicular to the direction of the fiber, while the *a* and *b* axes are in completely random orientation. Figure 28 shows the calculated curve and an experimental curve obtained by measuring the relative intensities of a typical photograph with a densitometer. It will be seen that the maxima and the minima of the curves coincide and that the shapes of the two curves show sufficient agreement to substantiate the fundamental assumption. The departure of the experimental from the calculated curve is simply a measure of the departure from perfect orientation, to be expected in such biological material.

With drying the large-spacing pattern of medullated nerve changes in an interesting manner. Equatorial points are to be distinguished at 140 and 71 Å. and a ring with equatorial accentuation appears at 43 Å. (Fig. 29). This behavior indicates that drying causes a separation of lipoidal components. In the fresh condition the lipoids appear to be associated in a single type of fluid crystal, presumably of the smectogenic type. With drying this or-

[6] The theoretical curve of Figure 28 was calculated from the relation:

$$I = \sqrt{\frac{1 - \cos^2\beta \cos^2\frac{\alpha}{2}(2 - \cos^2\beta)}{1 - \cos^2\frac{\alpha}{2}\cos^2\beta}}$$

in which α is the angle of scattering and β is the angle which expresses the departure of the scattering from the meridian. I is an intensity relative to the intensity for $\beta = 90°$. The Bragg requirement $n\lambda = 2d \sin \alpha/2$ determines α for any given d. The calculated curve of Figure 23 is actually for $\alpha = 10°$, and is therefore sufficiently close to that for $d = 4.7$ Å. to which the experimental curve refers.

AND IN LIPOID AND PROTEIN EXTRACTS OF NERVES

Wet Lecithin	Dry Lecithin	Cholesterol Powder Diagram (Principal Rings)	Wet Lecithin-cholesterol Mixture	Dry Lecithin-cholesterol Mixture	Nerve Lipoids Spun into Acetone	Nerve Protein Fibers
		3.55 mfR			3.34 fR	
			3.80 Å. fR	3.80 Å. fR		
			3.90 ffR	3.88 ffR		
	4.22 Å. sR				4.18 sR	
4.6 Å. sR	4.65 sR		4.77 mfR	4.75 mfR	4.62 mR	4.8 mR
		4.97 Å. sR	5.02 mfR	4.98 mfR		
		5.28 sR	5.25 fR	5.13 fR	5.18 fR	
			5.47 mfR	5.37 mfR		
			5.62 mfR	5.55 mfR		
		5.95 sR	6.00 sR	5.91 sR		
			6.55 mR	6.48 mR		
	7.2–10.1′ fR	8.2–11.0′ fR			7.2–10.3′ fR	
						9.1–11.5′ ssR
18.3 ffR		17.5 mR	17.1 fR	17 ffR	15–16# fR	
31.7 mR		34.8 sR	34.6 sR	34.5 mR		23 mR
	44–50# ssR			50 sR	Not Photo-graphed	48 sR
63.3 ssR			68.7 ssR			
126 mR						

Figures given show variation in center of intensity.

* The spacing is probably multiple.

Intensities are indicated very roughly and should be compared with caution between different columns and between widely separated portions of the same column.

ganization is disrupted and individual components behave differently, some remaining well oriented (140 Å.—cholesterol-rich fraction?), others being disoriented (43 Å.—phosphatids?). This separation of lipoidal components is indicated also by the change from an indistinct ring with meridianal sickles at 4.6–4.8 Å. to a series of rings each with meridianal sickling, to which reference has already been made. This behavior may be observed also in mixtures of single components. Table I shows the effect in the case of a lecithin-cholesterol mixture. Lecithin and cholesterol were dissolved separately in hot chloroform, mixed, and evaporated to dryness. The dry lipoids were then rubbed up with water and the resulting paste smeared onto the glass stirrup of the moist chamber and placed before the pinhole for radiation. After obtaining a photograph at large specimen-to-film distance the stirrup was removed from the moist chamber and, without disturbing the material, placed in a desiccator. After drying, a large-distance photograph was again made. A similar set of photographs was obtained from lecithin alone. The results are shown in Table I, while Figures 30 to 33 are the patterns obtained.[7]

From these results with wet and dry nerves, extracted nerve lipoids, pure lipoids, and with mixtures of pure lipoids it is obvious that the patterns will depend greatly upon the state of hydration and on the percentage composition of the mixture being radiated. This makes it extremely difficult to reproduce nerve patterns exactly by means of artificial mixtures, particularly as regards the large spacings. It is also difficult to attempt to identify any single lipoid in nerve by means of a characteristic spacing, since association with other lipoids changes the behavior of the individual components. While these difficulties are realized, certain points appear reasonable, and these will now be discussed, although owing to the limited knowledge of the chemistry of the lipoids the conclusions are to be regarded as tentative.

As has been stated, the lipoids of the myelin sheath appear to be organized as a mixed fluid crystal, presumably smectogenic in type. The dimensions of the unit aggregate may be placed tentatively at from $4.7 \times 9.4 \times 171$ Å. The *a* and *b* dimensions are reasonable values for the thickness of aggregates containing, in cross-section, four phosphatid molecules arranged in two "puckered" planes. The 171 Å. spacing in the *c* axis of the aggregate is presumably caused by an end-to-end association of eight lipoid molecules which are astonishingly well oriented radially, as brought out in Figure 28 and the discussion above.[8] It is highly desirable to know whether all the various lipoids of the myelin sheath asso-

[7] The spacings from 3.8 to 6.5 Å. for the lecithin-cholesterol mixture (Columns 11 and 12, Table I) are apparently not entirely comparable to those of the nerve lipoid pictures, probably in large part because of the fact that the mixture employed was rather rich in cholesterol. Thus these spacings are comparable in both dry and wet condition, presumably being ascribable to cholesterol-rich liquid crystal combinations of the two substances. Only at large spacings does the separation of lecithin from the cholesterol become apparent, with orders of a 68.7 (or multiple thereof) *c* spacing becoming, upon drying, rings typical of dry lecithin and cholesterol as observed from each in the pure condition.

[8] The 4.7 Å. spacing represents the dimension perpendicular to the planes of the "flat" sides of the single molecules, while the 9.4 Å. spacing is that of the width of the pairs of "leaflet" molecules. Thus, with eight molecular lengths forming the *c* dimension, the unit aggregate contains 32 molecules in all. It might be argued that the meridianal accentuations at 4.7 and 9.4 Å. are orders of the same spacing, hence the view presented above must assume a coincidence by which the strong 4.7 Å. ring is composed of second order reflections from a 9.4 Å. spacing and first order ones from the 4.7 Å. dimension. Such a coincidence seems reasonable from the consideration of the unit given above, and particularly in view of the observation that lecithin upon drying shows a separation of this ring into two components. Just why this recurrence of structure in the *c* direction is observed every eight molecules is not clear, but one might suppose a repetition, with this frequency, of a definite order of various types of molecules (including also cholesterol, sphingomyelin, or cerebrosides); or it is possible that unit aggregates or groups of them may be arranged at random in planes much as single molecules are considered to be arranged in smectic fluid crystals. The distance between such plane boundaries would then be 171 Å. Assuming random orientation of such aggregates about their *c* axes, which are usually radially oriented, the theoretical curve of Figure 28 shows that any dimension perpendicular to the *c* axis (*i.e.*, both *a* and *b* spacings) will be represented by meridianal accentuation, as is observed.

ciate to form this characteristic fluid crystal type or whether only a few of the lipoids are so associated, the remainder being distributed at random or forming a multiplicity of fluid crystal types, none of which is sufficiently often reproduced to give rise to diffraction patterns. If the myelin sheath is made up of concentric layers of these leaflet fluid crystals, each having a thickness of eight molecules, or 171 Å., there would be something less than two hundred such layers even in the thickest myelin sheath and perhaps only of the order of several dozen in thin sheaths. It is, of course, not impossible that the actual aggregate has a c dimension some multiple of 171 Å. Our present information merely tells us that 171 Å. is the smallest value, but it is entirely possible that subsequent work either with longer wave lengths, longer distances, or both may reveal this higher organization. We have indeed observed diffraction phenomena with the Spierer lens which indicate a higher organization of the myelin sheath, but the difficulties of interpretation of the results with this method appear insurmountable at present.

That this high degree of organization of the myelin sheath must be of physiological significance is patent. Omitting for the present any discussion of the bearing which this structure may have on the electric resistance, permeability, and polarizability of the myelin sheath, we should like to make only one point of application. It has been found (25) that nerve may be dried to a certain point (loss of over 60 per cent of its water) without irreversible loss of irritability. Further drying makes it impossible to restore irritability by subsequent soaking in Ringer solution. From the above considerations it is not impossible that the limits of reversibility are set by the ability of the crystals, which have segregated upon drying, to reorganize into the original mixed crystal type. This and other physiological consequences of this organization are being investigated.

Non-medullated nerve, fresh or dried, produced no pattern in the large spacing range. Since we have come to regard the lipoids as responsible for the easily obtainable large spacings, this means that the lipoids of lobster and crab nerve are not sufficiently oriented to produce diffraction. Analysis of lobster nerve (3), however, shows that sufficient lipoid is present to produce a pattern if it were oriented. From this it would appear that the chief difference between the lipoids in the axis cylinder and those in the myelin sheath concerns the degree of orientation and organization.

Since the work of Göthlin (7) it has been known that certain forms of non-medullated nerves, the so-called metatropic nerves, to which class lobster nerve belongs, can by treatment with glycerine be made negative in birefringence instead of positive, the normal condition. According to Göthlin, this reversal of birefringence is due to orientation of lipoid molecules produced by the transversely directed tension which accompanies glycerine dehydration. The reversal is due to lipoids because the effect cannot be accomplished if the nerve had been extracted with lipoid solvents before the glycerine treatment, and because negative birefringence in biological objects is produced as a rule by lipoids. Since preliminary extraction with acetone also prevents the glycerine reversal, Göthlin assumed that cholesterol is the lipoid specifically concerned. We have extended these observations and have found that the reversal may be accomplished even after extraction of all nerve proteins except neurostromin (23).

Since the diffraction method serves to reveal lipoid orientation we next studied the glycerine reversal by this method. Lobster nerves were soaked for long periods in glycerine and, after preliminary test to prove that the birefringence was negative, the nerves were blotted free of superficial glycerine and radiated. The photographs revealed mutually perpendicular sickles at about 35 Å. and 4.13 Å. These results are difficult to interpret since the 35 Å. is typical of cholesterol while the 4.13 Å. is typical of lecithin. They substantiate Göthlin's view that glycerine causes an orientation of

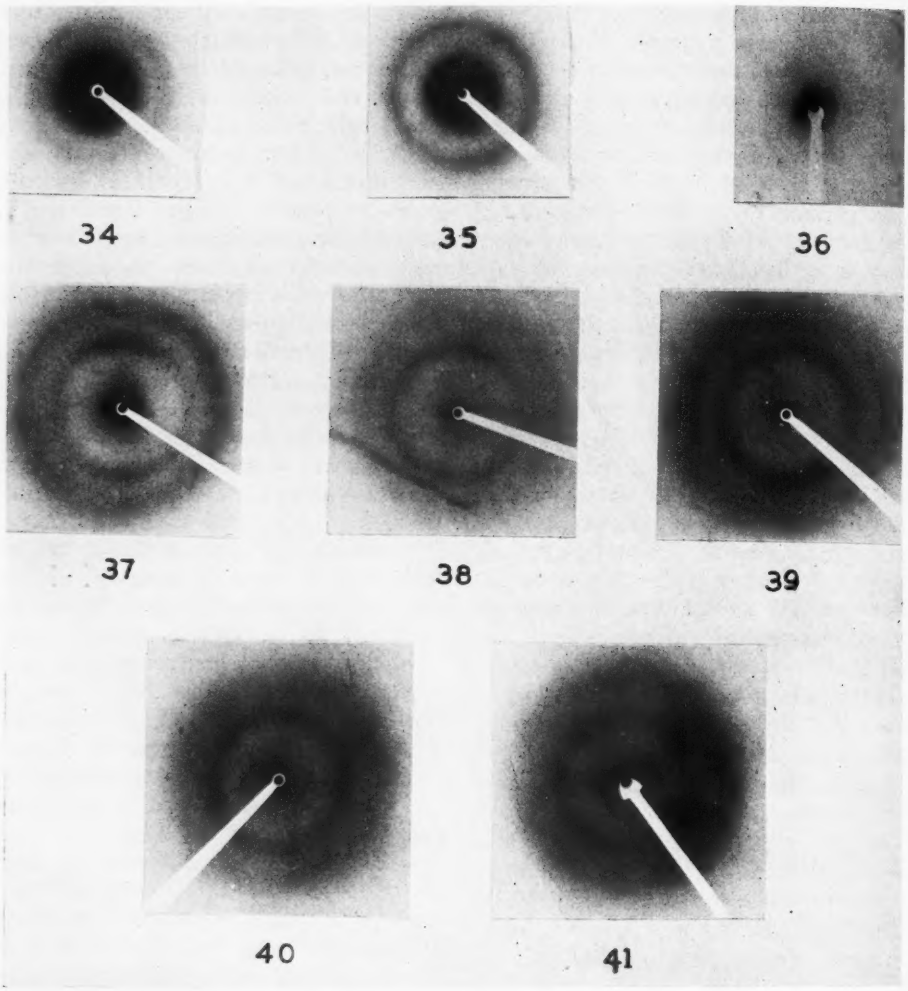

Plate 5. Fig. 34. Artificial fiber made by spinning cow spinal cord neurostromin into acetic acid containing 60 per cent alcohol and dried. D = 3.0 cm. Fig. 35. Artificial fiber made by spinning neutral-soluble nucleoprotein extracted from dried lobster claw nerves into acetic acid containing 40 per cent alcohol and dried. D = 3.0 cm. Fig. 36. Same as Figure 35 except that D = 8.90 cm. Fig. 37. Fresh frog sciatic heated to 42° C. for 15 min. Action potential was unaffected by the heating. D = 3.0 cm. Fig. 38. Fresh frog sciatic heated to 44° C. for 15 min. Action potential was reduced 78 per cent by the heating. D = 3.0 cm. Fig. 39. Fresh frog sciatic heated to 46° C. for 15 min. Action potential extinguished by the heating. D = 3.0 cm. Fig. 40. Fresh frog sciatic heated to 70° C. for 1 min. Shortening = 48 per cent. D = 3.0 cm. Fig. 41. Fresh frog sciatic soaked for one hour in 2M NaCNS at 31° C. Shortening = 60 per cent. D = 3.0 cm.

lipoid molecules but indicate that phospholipids, as well as cholesterol, may be involved in the effect.

Proteins of Nerve.—As pointed out above, while the pattern of fresh nerve appears to be explicable on the basis of lipoids exclusively, that of dried nerve contains spacings not so far found in lipoids. To identify this portion of the pattern was the next problem.

The protein chemistry of medullated nerve is at best only poorly understood and that of non-medullated nerve practically uninvestigated. It, therefore, became nec-

essary to do preliminary work upon this phase of the problem, particularly because of the lack of information concerning non-medullated nerve, which is representative of axis cylinder material generally. It was found (23, 3) that the soluble proteins of cow spinal cord are similar to those of lobster claw nerve and consist essentially of two nucleoproteins, one soluble in neutral and slightly alkaline solutions and the other (neurostromin) soluble at a *p*H of about 13; globulins appear to be absent. The possibility of another protein soluble at *p*H 14 or greater, perhaps collagenous in nature, and present in relatively small amounts has not been ruled out. Spun into an alcoholic solution of acetic acid (*p*H = ca. 5.0) from a capillary pipette, both neucleoproteins form threads which show weak positive birefringence. Upon drying, these artificial fibers become strongly positively birefringent and to some extent resemble dried lobster nerves, except for the fact that it has so far been impossible to cause them to swell in water or to show strong thermal shortening.

Radiated at a distance of 3 cm. these protein fibers give patterns resembling those of dried lobster nerve. There is a diffuse but fairly intense ring at 9.1–11.5 Å. and another less intense ring at 4.7 Å. (Figs. 34, 35, and 11). Despite the relatively strong positive birefringence, there was little indication of preferred orientation in the diffraction patterns. This is doubtless due to the effect commonly encountered in the spinning of other fibers, namely, that a relatively small superficial portion of the thread becomes well oriented, giving rise to the birefringence, while the inner core of the fiber remains unoriented. All of the artificial fibers gave essentially the same patterns whether spun from the neutral or alkali-soluble extract either of cow spinal cord or lobster nerve.

Because of the similarity of this pattern to that of unoriented fibrin published by Katz and de Rooy (12), we were at first inclined to assume that both rings were due to protein. Subsequent long-distance photographs to reveal large spacings indicated, however, that this was not the case. Rings at 48 Å. and at 23 Å. obtained from fibers spun both from neurostromin and neutral-soluble extract showed the presence of lipoid (Fig. 36) and it, therefore, appears likely that the 4.7 Å. ring is due also to lipoid. This conclusion is strengthened by the fact that the 4.8 Å. ring, as well as the 48 Å. ring, appears fainter in fibers spun into 95 per cent alcohol than in those spun into 40 per cent alcohol. The protein from which the cow spinal cord protein fibers were spun had been extracted several times with benzene and alcohol and the very thin fibers were spun into alcoholic solutions. Yet sufficient lipoid remained to yield a clear-cut diffraction pattern.

These facts make it clear that the proteins are represented in the pattern of lobster nerve by the ring at 11.5 Å. This ring is diffuse and may lie anywhere between 10 and 14 Å., depending on the degree of drying, and shows no sign of orientation except in the case of slow alcohol dehydration and tension. Apparently under these conditions the tension and the very slow dehydration combine to preserve the orderly orientation of the protein chains.

The fact that dried motor roots and lobster and crab nerves, as well as sciatics, show equatorial sickles at 11–13 Å., together with the statement that lobster nerve contains no oriented connective tissue but consists almost entirely of axis cylinder (Boehm, 5), was previously interpreted as evidence that this spacing is due to oriented axis cylinder proteins (20). Recent work, particularly with non-medullated nerves, indicates that this view requires qualification. That the nucleoproteins, which are the principal protein constituents of the axis cylinder, might and almost certainly do contribute to this spacing may be concluded from the fact that when spun into fibers and dried these proteins yield a ring with a spacing of the same order of magnitude (9–11 Å.). However, connective tissue, if present, would give a similar pattern. Alcohol-dried, stretched lobster and crab nerves also show meridianal sickles at 2.8 Å. which might also be

expected of connective tissue. Moreover, among the medullated nerves, those with large amounts of connective tissue (cat and bull frog sciatics) show the equatorial sickles best—indeed, plain drying in a desiccator suffices in these cases—while motor roots show the points faintest. The question as to whether these sickles are produced by axis-cylinder proteins or whether connective tissue also contributes hinges to a certain extent upon the relative quantity of connective tissue in non-medullated nerve. Boehm gives no details of the planimetric method by means of which he arrived at the conclusion that crab claw nerves contain "ca. 0 per cent connective tissue and 0 per cent oriented connective tissue." We had always accepted this view because of the ease with which these nerves break apart into numerous strands in sea water. However, since we found his estimate of the lipoid content of these nerves to be inaccurate, we made an independent investigation of the histology of the leg and claw nerves of the lobster and crab. The nerves were fixed, sectioned, and stained as in the case of medullated nerves, with methods designed to differentiate connective tissue. It was found that, far from containing a negligible amount, these nerves probably stand somewhere between cat motor roots and cat sciatics in the relative abundance of connective tissue (Fig. 4). While there is no outer sheath comparable to the epineurium, each fascicle is surrounded by connective tissue and there is a thin layer of interfibrillary connective tissue between the individual fibers. Moreover, the outer sheath of each fiber stains like typical connective tissue. de Renyi (17), in describing single fibers of the lobster ventral nerve chain, states that the sheath is composed of a layer of easily removable fibers (connective tissue?) and an inner smoother layer containing nuclei (Schwann sheath?). We have corroborated these statements not only for the fibers of the ventral nerve chain but also for typical fibers of the claw and leg of lobster and crab. The outer connective tissue sheath is also positively birefringent and shows marked thermal shortening.

In view of these observations on the tissue which has been serving as a representative of pure axis cylinder, the diffraction evidence of oriented protein chains in the axis cylinder must be considered inconclusive. Even if it were possible to show that interfibrillary connective tissue when stretched and dried does not produce typical equatorial sickles at 11–13 Å., it would still be necessary to show that the fibrous sheath around each fiber also gives negative results. There can be little doubt but that the ring at 10–12 Å. in dried non-medullated nerve is produced principally by the nucleoproteins of the axis cylinder, but it has so far been impossible to bring crucial diffraction evidence for the orientation of these proteins.

Thermal Shortening.—Patterns were obtained from maximally shortened frog sciatics, motor and sensory roots, cat sensory roots, and lobster claw nerve. All pictures were made at a distance of 3 centimeters. For shortening of 50 per cent the usual effect is simply a decrease in the orientation of the entire patterns. The 15.5 Å. points become elongated into sickles or into a ring and the meridianal accentuation of the 4.7 Å. ring is decreased. This effect is due in part to the irregular folding of the myelin sheath shown to result from thermal shortening by Schmitt and Wade (21). When shortened nerves are examined with polarized light, the contorted myelin sheath shows regions of negative birefringence alternating with regions of positivity depending on the orientation of each portion of the sheath.

There is some indication that thermal disorientation of the lipoids may precede the major shortening process. This was brought out in an experiment planned to determine whether thermal inactivation of the irritable mechanism involves disorientation of the myelin sheath fluid crystals. Frog sciatics were placed in Ringer solution at 42, 44, and 46° C. for fifteen minutes. At the end of this period they were returned to Ringer solution at room tempera-

ture and their action potentials determined with the cathode-ray oscillograph. The action potential of the nerve subjected to 42° was the same as that before heating, that at 44° was reduced 78 per cent, and that at 46° was completely extinguished. Although the lengths were not measured accurately, no visible shortening was observed in any of the nerves. The diffraction pattern of the nerve at 42° was typical of sciatics at room temperature (Fig. 37). The 15.5 Å. equatorial spacing was represented by slightly elongated points and the 4.7 Å. ring showed marked meridianal accentuation. The large spacing close to the bead also showed strong orientation. The pattern of the nerve kept at 44° showed a decided decrease in orientation (Fig. 38). The 15.5 Å. points were elongated into definite sickles and the 4.7 Å. ring showed only slight meridianal accentuation. The nerve kept at 46° gave a pattern practically identical with that of nerves which had undergone maximal shortening by heating to 70°. The 15.5 Å. spacing is represented by a ring or by thin elongated segments of a ring and the large spacing appears to be equally disoriented; no meridianal accentuation is visible in the 4.7 Å. ring (Figs. 39 and 40).

Aside from concluding from this evidence that lower temperatures are required to disorient the fluid crystals of the myelin sheath than to cause shortening of the protein structures, it is tempting to infer that the cause of thermal loss of irritability is the disorientation of the lipoids. It has been found that the action potential of frog sciatics declines abruptly at 43–44° C. and becomes zero at 45–46° C. (24). That the orientation of the lipoids is not the sole cause of this failure, however, is shown by the fact that there is a similar abrupt decline in respiration and in dehydrogenase activity at approximately similar temperatures (19, 24).

The Effect of Reagents and Conditions on Nerve Patterns.—Sodium thiocyanate and dilute acid cause great swelling—shortening of medullated and non-medullated nerves (12). As is to be expected, this type of shortening, as well as thermal shortening, causes great buckling of the myelin sheath and a consequent disorientation of the diffraction patterns. Figure 41 shows a pattern of a frog sciatic which had shortened 60 per cent in 2M NaCNS. Similar patterns were obtained from motor and sensory roots both in thiocyanate and in M/100 HCl. There is a tendency for the spacing in these patterns to be somewhat larger than in those of fresh nerves, averaging 16.5 Å. instead of 15.5 Å. The reason for this is not clear.

Calcium excess is said to favor the precipitation out of neurofibrils in the axis cylinder of teased medullated nerves (6). To test this effect we soaked a nerve in isotonic calcium chloride solution. The pattern obtained from this nerve after one hour of soaking departed little from the normal. After twelve hours of soaking the pattern showed disorientation which might have been expected from such abnormal treatment.

In an attempt to bring out the protein structure of the axis cylinder we prepared frog sciatics in cytological fixatives known to preserve neurofibrils. Formol-Zenker solution and isotonic potassium dichromate were tried. Some of these nerves were dehydrated by running through the alcohols and others were radiated without dehydration. The patterns revealed nc new structures but on the contrary were indistinct and considerably disoriented. This disorientation has been observed in every case in which formalin was used as a preservative.

It is known that impregnation of lipoids with osmic acid abolishes their birefringence (18). We, therefore, treated nerves with osmic acid until quite black and studied the diffraction pattern with the remote hope that if the pattern of the lipoids is destroyed a typical protein pattern might become more apparent. The resulting pattern showed little of the 4.7 Å. ring and nothing of the 15.5 Å. spacing, but there was considerable general scattering about the primary beam indicating

the presence of large lipoidal aggregates probably in random orientation.

Because of the marked effect of polarizing currents, both upon the irritability of nerve and upon structure, we arranged to pass current through a frog sciatic during the radiation. At 22.5 volts a current of 2.5 milliamperes was passed continuously during the radiation period which lasted fifteen minutes. The pattern so obtained was one of the clearest and best oriented ever gotten from fresh sciatics. The equatorial points had a spacing of 17.5 Å. instead of the usual 15.5 Å. and the meridianal intensification at 9.5–10 Å. was more apparent than in the average pattern of frog sciatics. The significance of these effects is not clear at present.

The Effect of Asphyxial Block on Nerve Patterns.—Frog sciatics still attached to the gastrocnemius muscles were placed in M/500 NaCN in buffered Ringer solution until the nerve became non-irritable. Patterns obtained from nerves radiated in this condition appeared to be similar to the normal pattern, indicating that the primary course of asphyxial block is not a disorientation of the lipoids of the myelin sheath. The work of Boehm (5) and of Handovsky (9) indicates that lipoid soluble narcotics can disorient the lipoids reversibly. It appears from the work of the latter that chloroform narcosis causes the 4.7 Å. spacing to break up into several rings. It is conceivable that these rings are comparable to the rings described above, which appear as a result of stretching and drying and which are caused by a separation out of components of the fluid crystals of the myelin sheath. Since Handovsky does not state the spacings of these rings, it is impossible to determine this point. Further investigation along this line is highly desirable.

SUMMARY

1. The diffraction patterns of fresh and dried medullated and non-medullated nerves are described. Medullated nerves are represented by the sciatic, motor, and sensory roots of the frog and cat and by the corpus callosum of the cat; non-medullated nerves by the claw and leg nerves of the lobster and crab.

2. The pattern of fresh medullated nerve is probably due entirely to oriented fluid crystals of the myelin sheath, for it can be reproduced fairly completely in preparations made by rubbing up a benzene extract of spinal cord with water. The fundamental aggregate of these fluid crystals appears to have dimensions of 4.7 × 9.4 × 171 Å., the various lipoids being associated in a mixed crystal fashion. The *c* spacing lies radial and perpendicular to the long direction of the axon. This means that in thinly myelinated fibers the myelin sheath is composed of but relatively few layers of these oriented lipoids associated end to end.

3. With the exception of the equatorial sickles at 11.5 Å., the patterns of dried medullated nerve can be reproduced by dried extracted lipoids. Rings with spacings characteristic of phosphatids and of cholesterol can be identified in the pattern of dried nerve. Drying disorients certain of the components of the myelin, leaving others fairly well oriented.

4. Heating frog sciatics causes a disorientation of the lipoids which appears to occur at or about the same temperature at which the action potential is extinguished. Higher temperatures, which cause maximal shortening, have little further effect on the x-ray patterns.

5. Patterns of frog sciatics treated with cyanide until the action potential was blocked departed little from the normal.

6. To study the structure of the axis cylinder, lobster and crab leg and claw nerves were used. These nerves have in the past been assumed to represent pure axis cylinder, containing little or no connective tissue or lipoids. This assumption has been shown to be incorrect by chemical analysis and by histological investigation. The lipoid content may be as high as from 25 to 30 per cent of that of the white matter of mammalian brain. Connective tissue is by no means negligible; there is inter-

fibrillary connective tissue as well as fibrous material closely adherent to each fiber. There is also a sheath which appears to be comparable to the Schwann sheath. These facts greatly complicate the analysis of the axis cylinder since the proteins of the axis cylinder give spacings similar to those of collagen of the connective tissue.

7. Artificial fibers spun from the nucleoproteins of lobster nerves, though fairly strongly positively birefringent, indicate no orientation in their diffraction patterns. A ring at 9.1–11.5 Å. represents the proteins. Even though these fibers were spun from fat-extracted protein, rings at 48, 23, and 4.8 Å. represent the lipoid components.

8. Alcohol-dried lobster nerves show equatorial sickles at approximately the same spacing as that given by the nucleoprotein of the axis cylinder. This fact was originally interpreted as showing that the axis cylinder contains oriented protein micelles. This conclusion must be qualified in view of the demonstrated presence in these nerves of collagenous material which might be responsible for at least a part of the orientation.

9. Although lipoids are present in very appreciable quantities in lobster nerve, they give rise to no pattern in fresh nerve. However, if the nerve be treated with glycerine, which changes the birefringence from positive to negative, patterns may be obtained which demonstrate that the lipoids have become oriented. Preliminary experiments indicate that cholesterol and perhaps also the phosphatids are involved in the effect.

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SQUAMOUS-CELL CARCINOMA OF THE KIDNEY

REPORT OF FOUR CASES

By B. H. NICHOLS, M.D., Cleveland Clinic, *Cleveland, Ohio*

SINCE only 57 cases of epidermoid carcinoma of the kidney have been reported in the literature, and since a correct diagnosis has never been made prior to operation or necropsy, the following four cases are reported.

Case 1. The patient, a woman 41 years of age, was seen first on Aug. 10, 1924. She complained that for one month she had had chills, fever, profuse sweats, and occasional hematuria. Four years before, three stones had been removed from the left kidney, and one year previously a mass had been discovered in the right side which had rapidly grown larger and had become increasingly tender. At the beginning of the onset of the most recent symptoms, two small calculi had been passed which apparently came from the right side.

Physical examination revealed a large mass in the region of the right kidney, and roentgen examination confirmed the diagnosis of kidney tumor, but no calculi were seen on the left side.

Examination of the blood revealed 3,000,000 red cells, 22,000 white cells, and the hemoglobin was 60 per cent.

Cystoscopic examination revealed a nodular, cauliflower tumor about the size of a small walnut in which there were areas of engorgement and necrosis; this tumor was in the region of the right ureter. The ureteral orifice could not be identified, and no urine was seen to come from this kidney. No abnormalities of the left kidney or ureter were discovered. From this examination, the clinical impression was that the patient was suffering either from a tumor which involved the lower end of the right ureter with a resulting hydronephro-

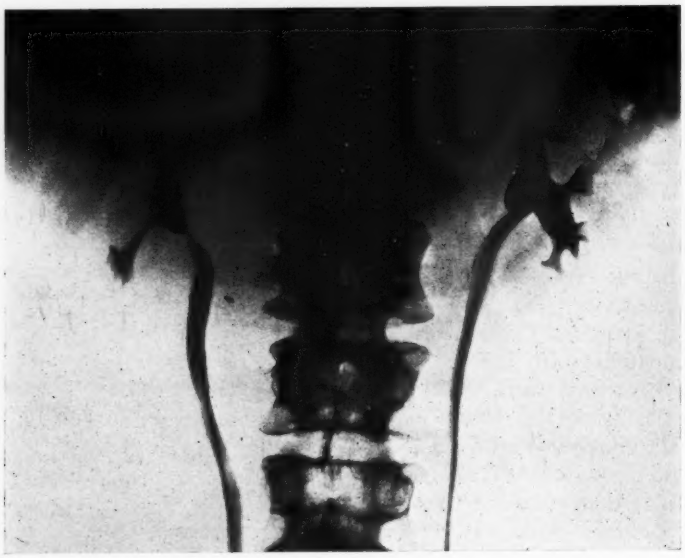

Fig. 1. Invasion of the kidney cortex by carcinoma extending from the kidney pelvis.

sis of the right kidney, or from a papillary carcinoma of the kidney with metastasis to the ureter.

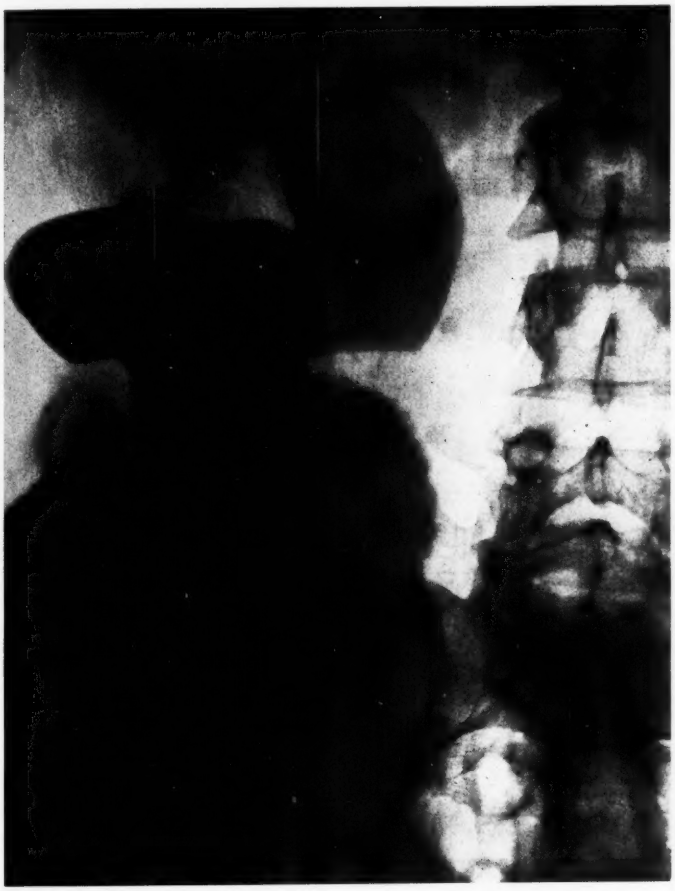

Fig. 2. Large renal calculi. The presence of malignancy was not determined, and a diagnosis of calculous pyonephrosis was made.

Due to the marked secondary anemia, a blood transfusion was given seven days after the patient was admitted to the hospital, and on the following day an exploration of the right kidney was made. A very large, adherent mass with a very thick capsule was discovered which contained thick, amber, syrupy fluid. Continuous drainage was established and, following operation, the patient's temperature returned to normal for six days. However, at the end of this time, chills, fever, and sweats occurred, the temperature rose, and the patient's condition gradually became worse until death occurred 28 days after the operation.

Necropsy revealed the right kidney to be markedly enlarged. It measured 9 × 5 × 5 cm., was partly firm, rather yellow in color, and contained abundant perirenal fat which was invaded by nodules. The pelvis of the kidney was dilated and filled with necrotic or degenerated material. A section presented a lobulated, yellowish red, moderately firm appearance, with marked degeneration and hemorrhage toward the central portion. The capsule was thickened, was stripped from the tumor with difficulty, and showed portions of

tumor growth which had eroded through the cortex. Marked thickening and involvement with the tumor growth was apparent around the ureter and vessels at the hilus.

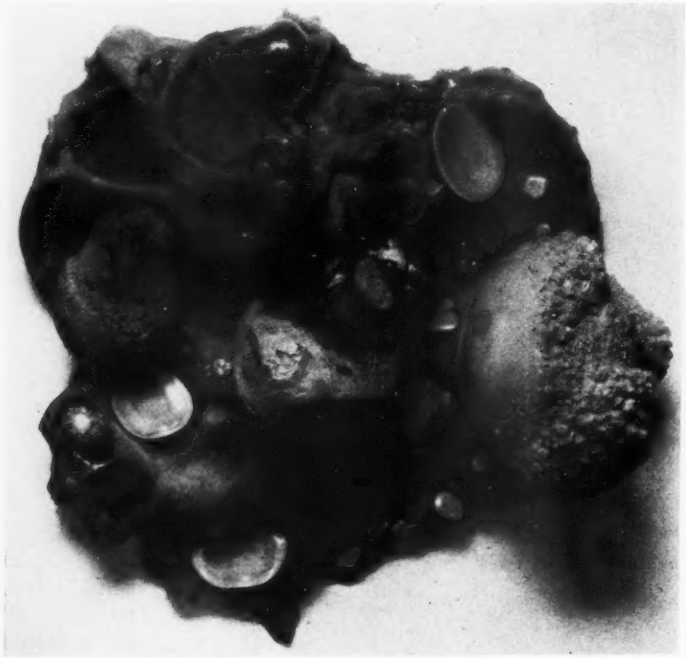

Fig. 3. Photograph of wax model of specimen.

Microscopic examination of several sections through different portions of the kidney revealed similar pictures, although marked degenerative changes were present in some portions. Of outstanding interest was the finding of large masses and columns of large, atypical, deeply chromatic, stratified, squamous epithelial cells, which grew in wild profusion in every direction and infiltrated deeply. Practically no renal structure was apparent in any area. Pearl formations, degeneration, and metaplastic cells, which probably were due to the degenerative changes, were seen in great abundance.

The pathologic diagnosis was squamous-cell cancer, probably arising from the renal pelvis.

Case 2. The patient, a man 52 years of age, was seen first on April 14, 1933. His chief complaint was of pain in the back, nocturia, and blood in the urine, present for 10 weeks. Blood first appeared in the urine after a sudden pain in the kidney.

Physical examination revealed no abdominal abnormalities except muscular spasm over the right lumbar region and tenderness to percussion in the same area. A slight lordosis was present.

Roentgen examination of the kidneys, ureters, and bladder showed no evidence of stones or of other pathologic change in the urinary tract. A pyelogram showed the left kidney to be normal except for a little rotation on the long axis. The lower calyx of the right kidney was seen to be normal, but there was marked compression and infiltration in the upper three-quarters of the kidney (Fig. 1). A diagnosis of carcinoma of the right kidney was made. Examination of the urine showed it to be loaded with red blood cells, and considerable albumin was present.

X-ray therapy was advised for this patient; he received six treatments which totaled about two thousand units. Three days after the last radiation treatment,

a right nephrectomy was performed. Pathologic examination revealed a tumor measuring about 7.5 × 6 cm., which was fairly well differentiated from the surrounding tissue, and was of a yellowish color. There were a few cortical cysts on the upper pole of the kidney. A section through the firm, rather friable tumor showed it to have a yellowish-gray, rather moth-eaten appearance. It was not well circumscribed, but rather diffusely infiltrated. The pelvis and calices were somewhat compressed by the tumor, but they were patent and contained no stones. The pelvic mucosa showed no gross ulceration, but the upper portion had a slightly roughened appearance. The ureters were patent, and the impression was that the growth was a liposarcoma of the right kidney. However, microscopic section of this tumor showed complete loss of the mucosa in some areas, metaplastic changes in the epithelium in still other areas, ulceration of the mucosa, and replacement by infiltrating squamous-cell carcinoma. The cells were of a large squamous type with some tendency to form keratohyalin material, but with no pearl-formation. The tumor had infiltrated diffusely outward from the renal pelvis. In one section, the renal artery was infiltrated and the lumen was occluded by tumor cells. Also, a large branch of the renal vein was invaded

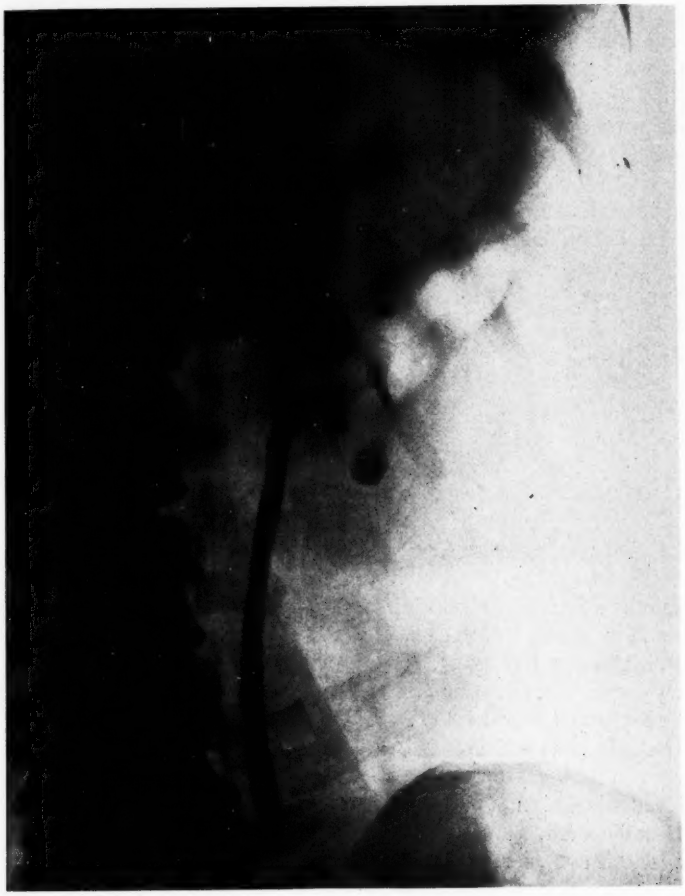

Fig. 4. Some obliteration of the caudal calyx. The question of the presence of tuberculosis was considered.

in a similar manner. There were numerous rather large areas of necrosis.

The patient remained well for three months and then returned complaining of pain in the left chest. Examination at this time showed metastatic nodules in both lungs. The patient died from metastases five months after operation.

Case 3. The patient was a man 51 years of age, whose chief complaint was of attacks of pain which had occurred at intervals during the past three years. Between the attacks, a dull ache was present which was referred to the abdomen and back. However, there had been periods of several weeks during which he had been without pain. During these three years, blood had been present in the urine at intervals, and there had been some nocturia. One year before this examination, the patient had had a fall and at that time a diagnosis of misplaced kidney was made.

Physical examination revealed a large, palpable right kidney which was somewhat tender and partially movable.

Roentgen examination of the kidneys, ureter, and bladder showed huge calcific deposits in the right kidney (Fig. 2). This kidney was very large, and the diagnosis of calculous pyelonephrosis was made. Examination of the urine showed many blood cells, and a large amount of albumin.

Nine days after admission, a right nephrectomy was performed. Gross examination of the specimen showed nephrolithiasis of the right kidney, hydronephrosis, chronic pyelitis, leukoplakia, and epidermoid carcinoma of the pelvis (Fig. 3). Microscopic section of this kidney showed a chronic inflammation of the cortex of the medulla, with ulceration of the mucosa and diffuse chronic inflammatory infiltration. In several of these sections, small areas and solid masses of rather large epithelial cells were present in the subepithelial layers of the mucosa. In some areas, there was complete replacement of the epithelium by keratinization and stratified squamous epithelium. There was no pearl-formation. In some of the sections, the entire pelvic wall was infiltrated to the peripelvic fat.

After operation, chest complications, thrombosis of the pelvic vessels and of the vessels involving the entire right leg occurred. The patient died one month after operation, and postmortem examination revealed metastatic carcinoma of the perirenal fat, right and left peri-aortic lymph nodes of the breasts and lungs, thrombosis of the pelvic veins, thrombosis of the pulmonary arteries, and multiple infarcts in the lungs.

Case 4. The patient, a woman 49 years of age, was seen first on June 15, 1932. Her chief complaint was of pain in the right side. Two years before this examination, she had had a severe attack of pain which lasted for a few hours. Two weeks later, a similar attack occurred, after which the patient was free from symptoms until five months before this examination. The pains began in the right side of the back, radiated around to the groin and to the upper thigh, and were of such severity that morphine was required to relieve them. For the five months previous to examination, the patient had had some constant pain. After the last attack, a large amount of blood was passed, and since that time hematuria had been present for a period of two or three days of each week.

Physical examination revealed no abnormalities. A plain plate of the kidneys, ureters, and bladder revealed no abnormality. A pyelogram showed a filling defect in the lower calyx of the right kidney which it was felt might be due to incomplete filling, a blood clot, or tuberculosis (Fig. 4). Examination of the urine failed to reveal the presence of acid-fast bacilli. However, blood and albumin were present in the urine. The clinical diagnosis was stone in the right kidney. The patient was advised to await any further development of symptoms. She returned again in June, 1933, eleven months after the first examination, and reported that hematuria had been present at intervals. A pyelogram made at that time showed a filling defect in the pelvis of the left kidney, and narrowing of the uretero-pelvic

junction, which suggested the presence of a neoplasm.

Nephrectomy was advised and the left kidney was removed. The specimen showed a papillary type of tumor. The lower section of the kidney was filled by a very hard, opaque, yellowish-white growth which was fairly well circumscribed and measured approximately 2 centimeters. A papillary tumor arose from the pelvis in the region of the lowermost calyx. The pelvic mucosa for the most part appeared thickened and edematous. The ureter was apparently normal. The diagnosis based on the gross examination was papillary carcinoma of the kidney. Microscopic section of the tumor near the uretero-pelvic junction showed a somewhat papillary growth of pelvic epithelium, with invasion of the underlying submucosal and peripelvic tissue by small and large solid masses of squamous epithelial cells. The tumor cells varied greatly and showed very little keratinization. Mitotic figures were scarce. The growth was diffuse, infiltrated the medulla of the kidney, and extended into the cortex.

One year later the patient had no symptoms of recurrence or metastases of the tumor.

Fig. 5. Roentgenogram made 11 months after Figure 4. Complete obliteration of the caudal calyx is seen, and a diagnosis of carcinoma of the kidney pelvis was made.

COMMENT

Gilbert and MacMillan (1), in a very thorough discussion of the subject, reviewed all cases of squamous-cell carcinoma of the kidney pelvis reported in the literature, and they were able to collect 55 cases and added two cases of their own.

The four cases presented here demonstrate the difficulties encountered in making a correct diagnosis of epidermoid carcinoma of the kidney pelvis.

The average age of these patients was 48 years. There were two women and two men. Hematuria was present in all four cases. Stones in the kidney were present in two cases, and pyonephrosis was seen in two cases. In two cases a palpable mass was present. Three patients gave a history of pain and one of injury.

There were no clinical findings in these cases which in any way might be considered to be characteristic of epidermoid carcinoma. All cases were subjected to

roentgen-ray examination. In the first case, a definite diagnosis of kidney tumor was made from the appearance of the kidney as observed on the steroscopic roentgenogram of the urinary tract. This was in fact the only definite evidence of kidney tumor, and it established the fact that the palpable mass was connected with the kidney. In the second case, again the presence of a kidney tumor was determined by the pyelographic film which showed a tumor of the pelvis of the kidney with invasion of the cortex. This was interpreted properly as a carcinoma of the kidney.

In the third case, the roentgen examination was of no value in determining the presence of a carcinoma of the kidney because of the huge calculi in this kidney and a diagnosis of calculous pyonephrosis was made. Pyelographic findings led us to believe that tuberculosis of the kidney pelvis was present in the fourth case; however, 11 months later another pyelogram definitely established the diagnosis of carcinoma of the kidney. In none of these cases was epidermoid carcinoma of the kidney pelvis suspected, and only after microscopic study of the tumor was such a diagnosis made.

Case 3 well illustrates the presence of squamous-cell cancer of the kidney in the presence of large calculi of the kidney associated with inflammation and leukoplakia, and in the presence of such findings, one should suspect the possibility of such a tumor at the time of the examination. In this case there was a history of injury which may be of significance as an etiologic factor. However, the large multiple calculi may be considered as the most logical contributing factor because of irritation and the production of leukoplakia. It is interesting to note that Nicholson (2) reported 16 cases of squamous-cell carcinoma of the gall bladder in 15 of which gallstones were present. This tends to confirm the theory that chronic irritation is an etiologic factor in the production of squamous-cell carcinoma. Infection in this series of cases was not of sufficient frequency and duration to be considered as important as an etiologic factor.

No cures were secured in three of the cases reported which indicates the necessity for early diagnosis. In the fourth case, pathological examination showed early squamous-cell changes, and this patient is alive, two years after operation. Again, the importance of early diagnosis is emphasized, that is, a diagnosis of kidney tumor and prompt treatment by removal of the kidney which preferably is preceded by radiation of the kidney. The one case in which this procedure was followed resulted in failure; however, in the presence of a tumor as highly malignant as is epidermoid carcinoma of the kidney, we feel that all available remedial agencies possible should be used. Roentgenologic examination of the chest should always be made in the presence of a suspected kidney tumor. Chest metastases occurred in 50 per cent of our cases.

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THE SIGNIFICANCE OF WEDGE-SHAPED DEFORMITY OF THE BODY OF THE VERTEBRA[1]

By G. W. GRIER, M.D., *Pittsburgh, Pa.*

THE title refers to a narrowing of the anterior margin of the vetebral body so that, in a lateral roentgenogram, it appears to be triangular in shape instead of rectangular as is normal. This deformity occurs when the body of the vertebra becomes fragmented as in fracture crush, or when the bone becomes sufficiently softened from pathologic processes so that the body weight compresses the vertebra from above downward. Under these circumstances the effects of compression are greater in the anterior portion of the vertebra than in the posterior portion, producing the wedge-shaped deformity under discussion. This deformity is attributed to two factors:

1. The center of gravity of the body with the individual erect falls in a plane anterior to the spinal column. Therefore, the downward thrust of the body weight would be greater at the anterior margin of the vertebra than at the posterior.

2. The interlocking processes between the vertebræ, and, in the dorsal region, the ribs also tend to support the posterior margin of the vertebra and prevent its collapse.

I am inclined to attach more significance to the latter of the hypotheses. Many times I have observed cases of fracture crush of the body of the vertebra in which the roentgenogram made within a few hours of the accident shows the typical wedge-shaped deformity. As the patient had not been erect during the interval between injury and x-ray examination, it is obvious that body weight in the erect posture had no part in producing the deformity. Since we know, then, that the

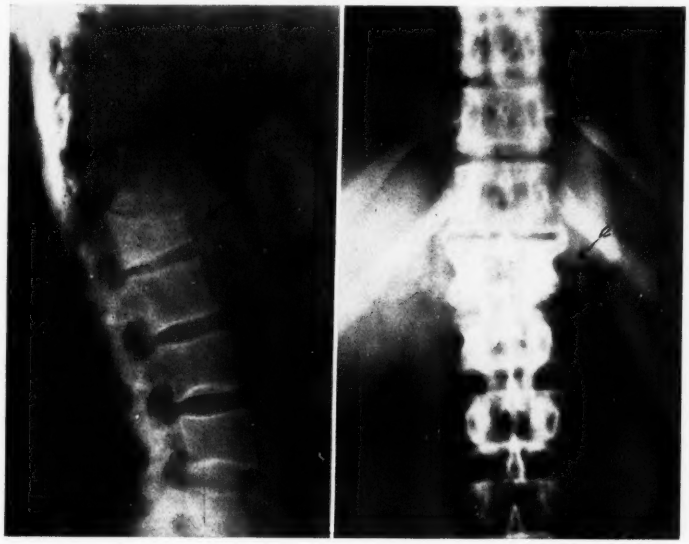

Fig. 1. In fracture crush of the body of a vertebra, in addition to the compression of the anterior border of the vertebra as demonstrated in the lateral view, there is usually a widening of the vertebra laterally and a narrowing from above downward in the anteroposterior view. Intervertebral space is not involved.

[1] Read before the Pittsburgh Academy of Medicine, January, 1933.

Fig. 2. When the nucleus pulposus is ruptured by traumatism, the swelling of the nucleus causes a notched appearance on the opposing surfaces of the bodies of the vertebræ. The nucleus is also often displaced, as in the case shown here.

deformity can occur in the absence of factor No. 1, it seems questionable what part this factor plays in producing the deformity.

Let us consider now the differentiation between the various conditions producing this deformity. Beginning with fracture, we find that this is the only condition in which the deformity is due to fragmentation. However, this does not help us much since it is extremely seldom that one is able to distinguish the various separate fragments. Naturally a history of injury is very suggestive, but cannot be relied on too much, as fracture can occur from an injury which the patient may consider too trivial to mention, or the history may be unreliable from other causes. It is well to remember that in fracture the vertebra is often increased in width from side to side, as well as narrowed from above downward, and that a sharp angulation both laterally and anteroposteriorly usually occurs at the site of fracture. By far the most common site of fracture is in the last two dorsal and first two lumbar vertebræ. In healed fracture, in cases in which the history is unreliable, the location and widening, with lateral angulation, are the most reliable signs. Recognition of callus cannot be relied upon. As a matter of fact, new bone deposit is much more common in certain inflammatory conditions than in fracture. The intervertebral space is usually normal in fracture.

Occasionally injury to the cartilage may occur, manifested by compression of the cartilage, with narrowing of the intervertebral space. The cartilage may become fractured, producing a similar effect. Injuries to the cartilage may result in disruption or dislocation of the nucleus pulposus, a very tough, elastic, round or oval body located about the center of the cartilage. Its function is to act as a fulcrum on which the bodies of the vertebræ pivot during anteroposterior bending of the spine. Violent injury may produce fracture of the cartilage, with disruption of the nucleus, which swells, due to its elasticity. It may be thrust against the opposing surface of the vertebra, producing a depression in the bone corresponding to the size and shape of the nucleus. Sometimes the nucleus is displaced backward in the cartilage and this displacement widens the intervertebral space posteriorly and interferes with the normal motion between the vertebræ. Accurate information regarding injuries to the cartilage are rather meager, and it seems certain that many such injuries have gone unrecognized in the past. The studies of Schmorl have recently stimulated interest in this field, and it seems probable that instructive observations and experiences will soon make their appearance in medical literature.

Another lesion of the vertebra occurring as a result of injury and one which has caused considerable confusion is the so-called Kümmel's disease. Kümmel reported this condition before the discovery

of x-rays, his knowledge of the condition being based on autopsy findings. Briefly, the condition is one of compression of the anterior margin of the vertebra. Kümmel thought the condition was due to a traumatic osteitis, with decalcification and softening of bone and a consequent deformity. The deformity does not make its appearance until two or more months following the injury. Many authors since Kümmel have thought that the condition was really an unrecognized fracture crush, while others agree with Kümmel. It is, of course, necessary to have x-ray films showing a normal vertebra immediately after the accident in order to identify Kümmel's disease. As the accident is often trivial, x-ray films are usually not made. However, symptoms persisting, later x-ray examination shows the deformity. It is this peculiar set of circumstances which has produced so much confusion in Kümmel's disease. However, a sufficient number of cases have been observed in which roentgenograms, made immediately following injury, were normal, while others, made later, showed the typical deformity, so that there can be no doubt of the identity of this disease. I have observed one such case and many others in which the history was identical with Kümmel's disease, though the immediate x-rays were not taken. I believe the process is one of decalcification and not of unrecognized fracture. The deformity of fracture occurs immediately following injury, and I can see no reason why x-ray films taken at that time should not show it. I believe this condition occurs much more often than is generally believed. A study of the lateral films of the spine in any x-ray department is sure to reveal a number of cases in which one vertebra shows a wedge-shaped deformity. Investigation of such a case usually does not bring to light any history of serious injury, but the patient complains of pain in the back. As a matter of fact, the history is quite similar to the one *bona fide* case of Kümmel's disease I have observed personally. The only thing that is lacking is the normal x-ray film made after an accident—if this had been made, quite probably further x-ray examination would have been considered superfluous, so that

Fig. 3. Kümmel's disease: (*A*) Note slight compression of the anterior margin of the body of the first lumbar vertebra, and the concavity of the anterior surface. This film was taken six months after the accident. (*B*) Film taken immediately after the accident does not show these changes.

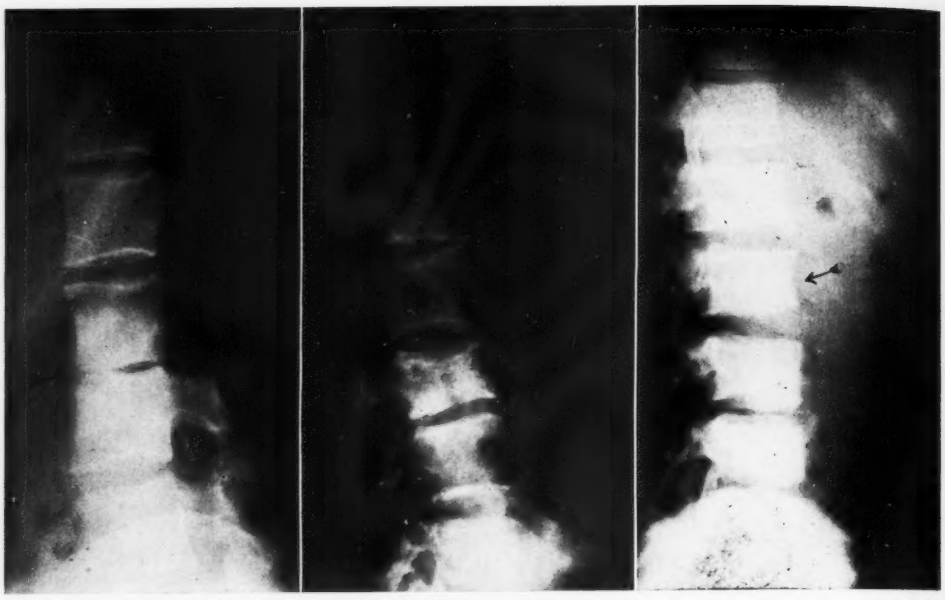

Fig. 4. Fig. 5. Fig. 6.

Fig. 4. This is a case of very early tuberculosis, selected to show the destruction of the cartilage which always precedes destruction of the bone. In a later stage the bodies of the vertebræ become destroyed and compressed along the anterior border.

Fig. 5. Beginning compression of the body of the third lumbar vertebra in a case of metastatic carcinoma. In a later stage, the body of this vertebra will become more completely destroyed.

Fig. 6. There are various changes seen in syphilis of the spine—sometimes localized areas of destruction, sometimes new bone formation. The case illustrated here shows compression of the body of the second lumbar vertebra, due to rarefaction from a generalized osteitis.

the solution to this problem does not seem to rest with the roentgenologist. In any event, I feel that wedge-shaped deformity of a vertebra should always be accepted as abnormal and requiring explanation. It may not have any more clinical significance than calcified tubercles in the lung, but it certainly is not normal and should be explained to the satisfaction of the clinician before a final diagnosis is made.

Wedge-shaped deformity due to congenital malformation is usually seen in the dorsal or lumbo-sacral region. In the dorsal region, the incomplete vertebra is practically always a lateral wedge and not an anteroposterior one. It is usually accompanied by a lack of symmetry, or the absence of a rib. The fifth lumbar vertebra is normally wedge-shaped, being wider in front than behind. In cases in which a sixth lumbar vertebra is present, this is also shaped like the normal fifth lumbar. Incidentally, the presence of this extra wedge-shaped vertebra in this location predisposes to spondylolisthesis.

In considering deformity due to softening of the body of the vertebra, we find the lesions fall into two groups:

1. General decalcification due to constitutional causes.
2. Local disease.

Under general decalcification may be classified:

Posture curve
Osteo-arthritis
Osteomalacia
Rickets
Hyperparathyroidism

Lesions due to local disease are:

Tuberculosis
Carcinoma
Syphilis
Paget's disease

Fig. 7. Osteochondritis may, as in this case, involve only one vertebra, when the lesion is very similar to Köhler's disease in the tarsal scaphoid. In other cases, there is a slight compression of a number of adjoining vertebræ, simulating a postural kyphosis.

Hodgkin's disease
Osteochondritis.

It is with some hesitation that I attribute the compression of a vertebra which occurs in posture kyphosis to decalcification. However, it seems to me that all the evidence would indicate that some softening of bone is present in these cases, both in the adolescent and in the aged. Probably no one will deny that decalcification and softening accompany the postural curvature which comes with senility, especially in cases in which this occurs in combination with osteo-arthritis. It is not customary to attribute the posture curve of youth to bone pathology, but when one considers that these children are practically all under par physically, it seems reasonable that the bones may be lacking in lime salts also and that the deformity of the vertebra is really due to a certain amount of softening and decalcification.

In osteo-arthritis, osteomalacia, and rickets, there is a general absorption of lime salts from the bones which results in compression of the bodies of the vertebræ, most pronounced along the anterior margins. The process usually involves the dorso-lumbar region first and, when other portions of the spine are involved, the changes are more marked in this location than elsewhere. In addition to the compression, cases of osteo-arthritis present bony deposits on the edges of the vertebra, which project as bony spur-like formations. These projections, together with the compression, change the anterior border of the vertebra from a plane surface to a

Fig. 8. In Hodgkin's disease, bone destruction in the spine is usually caused by pressure from enlarged lymphatic glands along the spine. In this case it is obvious that the lesion is a metastatic one involving the body of the first lumbar vertebra.

concave one. This spur formation is peculiar to osteo-arthritis and is not seen in osteomalacia or rickets. The interarticular cartilage is apt to be narrowed in osteo-arthritis. However, in osteomalacia the cartilage assumes a bi-convex shape, thought to be due to a swelling of the nucleus pulposus brought about by the great elasticity of the nucleus and the lessened resistance of the greatly softened bone of the vertebra on each side. In osteomalacia, the decalcification is extreme.

In rickets and in hyperparathyroidism, the changes are similar to those in osteomalacia, but usually not so extreme. The differentiation between the three diseases is made by other means than roentgenograms of the spine. Rickets, of course, occurs only in children. Osteomalacia and hyperparathyroidism differ clinically, and the roentgenograms of other bones show somewhat different characteristics.

In tuberculosis there is actual bone necrosis which may go on to complete destruction of the bodies of one or more vertebræ. The interarticular cartilage is involved early. It soon becomes narrowed from destruction and may disappear entirely. In healing, it is not unusual for the bodies of adjoining vertebræ to become fused. Abscess formation is of common occurrence and if the involvement is in the dorsal region, this will show on the roentgenogram. Tuberculosis starts in one vertebra only and spreads from there by continuity to neighboring vertebræ. This is in contradistinction to other processes, which often appear simultaneously in different locations. When tuberculosis heals there is recalcification, but there is no deposit of excessive new bone as in syphilis, gonorrheal, or typhoid infection. Occasionally, cases of tuberculosis are seen in which the involvement begins centrally, and collapse of the vertebræ does not occur until there is very extensive involvement.

Metastatic carcinoma may involve one or more vertebræ simultaneously. As a result of invasion of the bone by the malignant growth it becomes weakened and collapses, the typical wedge-shaped deformity following. The interarticular cartilage is not involved and the space between vertebræ is normal. Sometimes in metastasis from scirrhous carcinoma the invasion is so slow that the vertebra does not collapse but maintains its normal form, or perhaps becomes slightly compressed as a whole without assuming a wedge shape. There is no new bone formation in carcinoma.

In syphilis, as a result of osteitis, the bone becomes somewhat softened and compressed. The involvement is apt to be solitary, or limited to the vertebra immediately adjacent. The early appearance is quite like tuberculosis except that the cartilage is uninvolved. When the process heals, extensive deposits of new bone occur.

In Paget's disease the involvement is multiple, osteitis is present, and there is a generalized softening with deformity of several vertebræ. In addition, this process is characterized by localized deposits of excess calcium, which give the bones a mottled appearance. The differentiation of this disease is usually made by roentgenograms of the long bones, which present characteristic changes.

In late Hodgkin's disease, bone changes in the spine are not uncommon. They are usually due to pressure on the spine from enlarged paravertebral lymphatic glands. These changes are localized areas of destruction and not the wedge-shaped deformity we are considering. However, instances are occasionally seen in which metastasis undoubtedly occurs to the body of the vertebra and in these cases the involvement is exactly the same as in metastatic carcinoma. There is an extensive destruction of bone, the body of the vertebra collapses, and the typical deformity results.

Osteochondritis occurs in the adolescent. The process is a mild osteitis involving the cartilage, or the cartilage plate, the epiphysis, and the cartilaginous border of the vertebra. Slight erosion of the vertebra occurs, producing an irregular surface bordering on the cartilage. Softening of bone also occurs, with some compression of the anterior margin of the vertebra. One or

more vertebræ may be involved. The process is more apt to occur in the lower dorsal region. Healing usually takes place spontaneously, the deformity being permanent. Another manifestation of osteochondritis seen in young children involves only one vertebra and is similar in many respects to Köhler's disease of the tarsal scaphoid. The process is primarily an osteitis. There is, first, bone softening, with later compression of the body of the vertebra. The lesion heals by new bone formation, leaving the vertebra smaller, but more dense than normal.

INTENSITY AND DOSAGE NEAR RADIUM NEEDLES[1]

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From the National Research Council of Canada

Part I

INTRODUCTION

IT HAS been customary to describe radium treatments in milligram-hours, the product of the quantity and time of application of the radium. The number of milligram-hours required to produce the desired effects varies between wide extremes, depending on the distance of the radium from the tissue and other factors. Therefore, comparisons in milligram-hours without further information are of little significance except in questions of economy.

The practice of radiology is based on the supposition that similar results under similar conditions tend to follow similar physical disturbances. Therefore, it is sensible to discuss directly the disturbance—that is, the irradiation—rather than the milligram-hours necessary to produce it. The practice is growing of describing radium therapy in terms which are a measure of the actual amount of irradiation applied. Two units of the quantity of irradiation have been used for this purpose: the roentgen, which is familiar in x-ray therapy, and the milligram-hour per centimeter squared (abbreviated Imc.-hr.). Statement of the irradiation in these units, in addition to full description of radium needles and their position relative to the skin and the tumors, is a useful specification of the physical treatment.

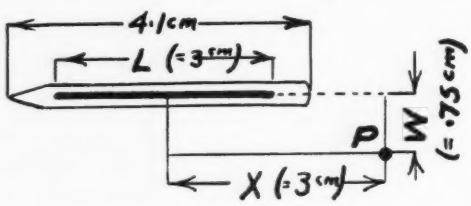

Fig. 1.

The "dose" at a point in the tissue is the number of roentgens or Imc.-hr. traversing the region of point during the irradiation. This quantity is not easily measured on every occasion. It is practicable, however, to select a number of arrangements of needles which are frequently used, to determine the dose near them, and to tabulate this information in convenient charts for ready reference in routine work. This has been done at the Radiumhemmet, Stockholm, the Memorial Hospital, New York City, and elsewhere (1). The charts which they have prepared are not always applicable in other institutions where needles are used of different design, and in different arrangements. This paper gives formulæ and graphs from which can be determined easily the dose at any point near any needles with sufficient accuracy for therapeutic purposes. It is possible to construct from this, dosage charts for combinations of needles with much less labor than is involved in the corresponding laboratory measurements, or in calculation from first principles. A useful set of charts may be prepared in a few hours.

Part I of the paper is restricted to the practical details of the method of determining the dose at a point near a radium needle or tube, and of preparing charts of the distribution of the dose near a combination of needles. Theoretical discussion of the derivation of the formulæ and data and other questions is given in Part II.

THE DOSE AT A POINT NEAR A RADIUM NEEDLE

The dose at a point P near a radium needle or tube is given by

[1] Presented before the Radiological Society of North America, at the Twentieth Annual Meeting, at Memphis, Tenn., Dec. 3–7, 1934.

$$D = \frac{MT}{L^2} f_1(1 - f_2(ks + k_1 w))$$

if expressed in Imc.-hr., or by

$$R = 8.6 \frac{MT}{L^2} f_1(1 - f_2(ks + k_1 w))$$

if expressed in roentgens.[2]

M in these formulæ is the quantity of radium element (not the radium compound) in the needle in milligrams. (Certificates of radium needles issued by the national laboratories do not usually state M directly. For example, the needle may be said "to emit radiation equivalent to 0.95 mgm. radium . . .," and a footnote on the certificate may state further that it is estimated that 5 per cent of the radiation is absorbed in the needle walls. For such a needle, therefore, M would equal 1.00 mgm.)

T is the time of exposure in hours.

L is the length in centimeters of the cavity in the needle (not the total length of the needle), which is filled with radium. If not known, it is easily found by making a contact print of the needle by its own radiation on x-ray film. A few seconds' exposure will produce a black line on the film which is only very slightly longer than L.

s is the effective thickness of the needle wall in millimeters. To sufficient accuracy it equals the actual thickness increased by 5/33 of the inner radius of the wall, *i.e.*, $s = r_2 - \frac{28}{33} r_1$. r_2 and r_1 are the outer and inner radii, respectively.

k is the absorption constant of the material comprising the needle wall, values of which are given in Table I.

f_1 and f_2 are numbers which depend on the position of the point. f_1 is obtained from Figure 2, and f_2 from Figure 4. f_1 and f_2 are plotted in terms of $\frac{x}{L}$ and $\frac{w}{L}$. The significance of these may be seen from Figure 1. L, as before, is the active length of the needle, w is the distance of the point from the axis of the needle, and x is its distance from the plane which cuts the needle axis perpendicularly through its center.

TABLE I.—ABSORPTION COEFFICIENTS FOR THICKNESSES OF MATERIALS IN MILLIMETERS

Aluminium	0.007/mm.
Lead	0.088
Platinum, Iridium pt.	0.139
Gold	0.140
Silver	0.043
Monel	0.021
Muscle, Epithelial tissue	0.0024
Bone	0.0055
Water	0.0026
Rubber (lead-free)	0.0023
Soft wood (pine)	0.0013
Hardwood (ash)	0.002
Paraffin wax	0.0022
Glass (lead-free)	0.007

Part of Figure 2 is reproduced on large scale in Figure 3.

k_1 is the absorption coefficient of the biological tissue. For epithelial tissue and muscle, $k_1 = 0.024$ if w is given in centimeters. Within 1 cm. of the needle, $k_1 w$ may be considered negligibly small and may be omitted.

Example:—The 10 mgm. needle shown in Figure 1 was applied for 10 hours. It is required to find the dose at the point P, 0.75 cm. from the axis, and 3.0 cm. from the central plane.

Wall material, iridium platinum; hence from Table I:

$$k = 0.14/\text{mm.}$$

Outside diameter, 3 mm.; inside diameter, 2 mm.; therefore

$$s = \frac{1}{2} \times 3 \text{ mm.} - \frac{28}{33} \times \frac{1}{2} \times 2 \text{ mm.} = 0.65 \text{ mm.}$$

Length of radium cavity, $L = 1.5$ cm.; $w = 0.75$ cm.; $x = 1.5$ cm.;

Therefore, $\frac{x}{L} = 1$; $\frac{w}{L} = \frac{1}{2}$.

Referring to Figure 2, it may be seen that the co-ordinates

[2] See Footnote 6, p. 178.

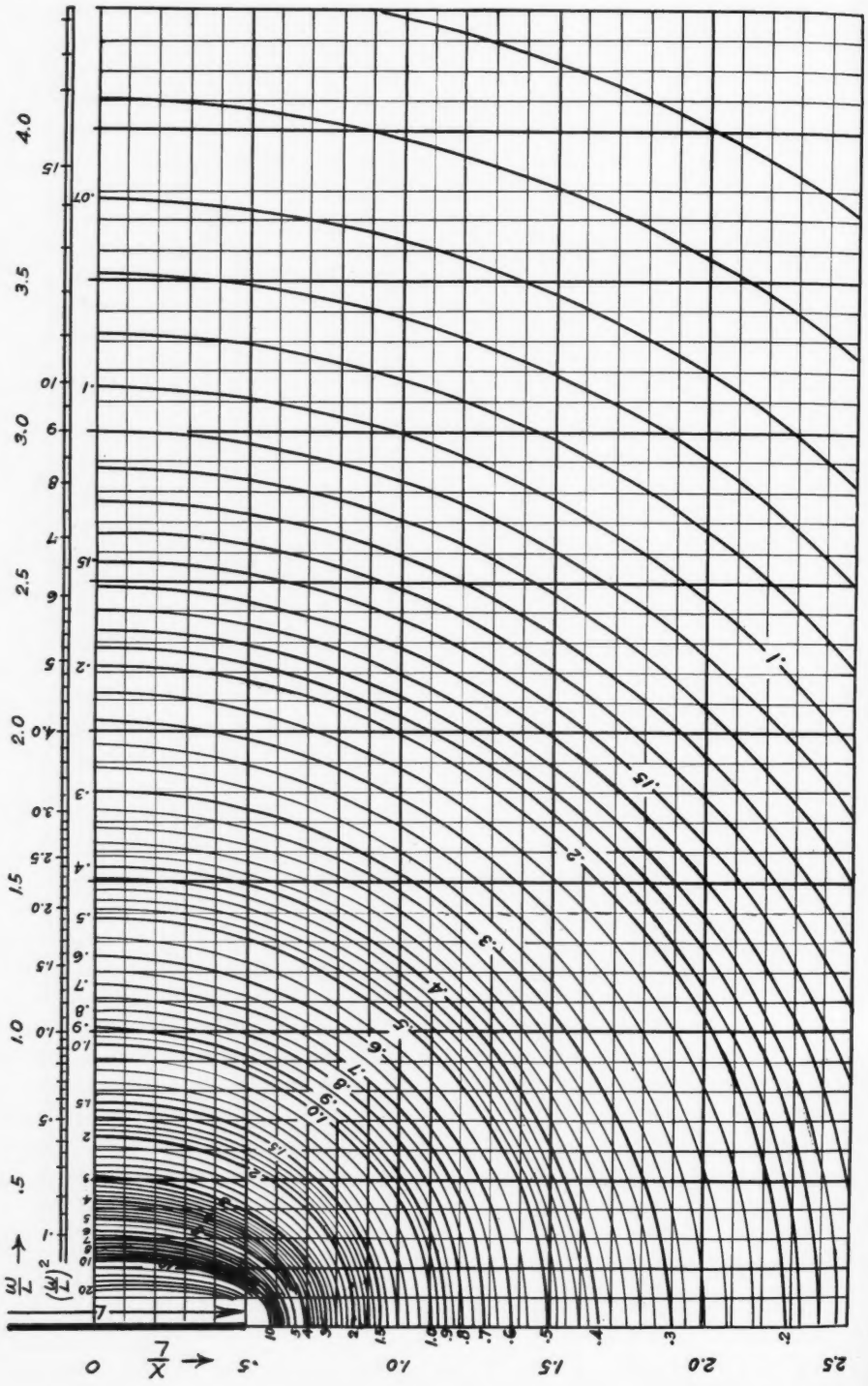
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0
.5
1.0
1.5
2.0
2.5
$\frac{W}{L^2}$
$\frac{L}{X}$
1.
.15
.2
.3
.4
.5
.6
.7
.8
.9
1.0
1.5
2
3
4
5
6
7
8
9
10
15
20

Fig. 2.

$\frac{x}{L} = 1$ and $\frac{w}{L} = \frac{1}{2}$ intersect at the curve $f_1 = 0.94$.

might be based on the determination of the dose at 20, 40, or more points. This requires considerable calculation. Much

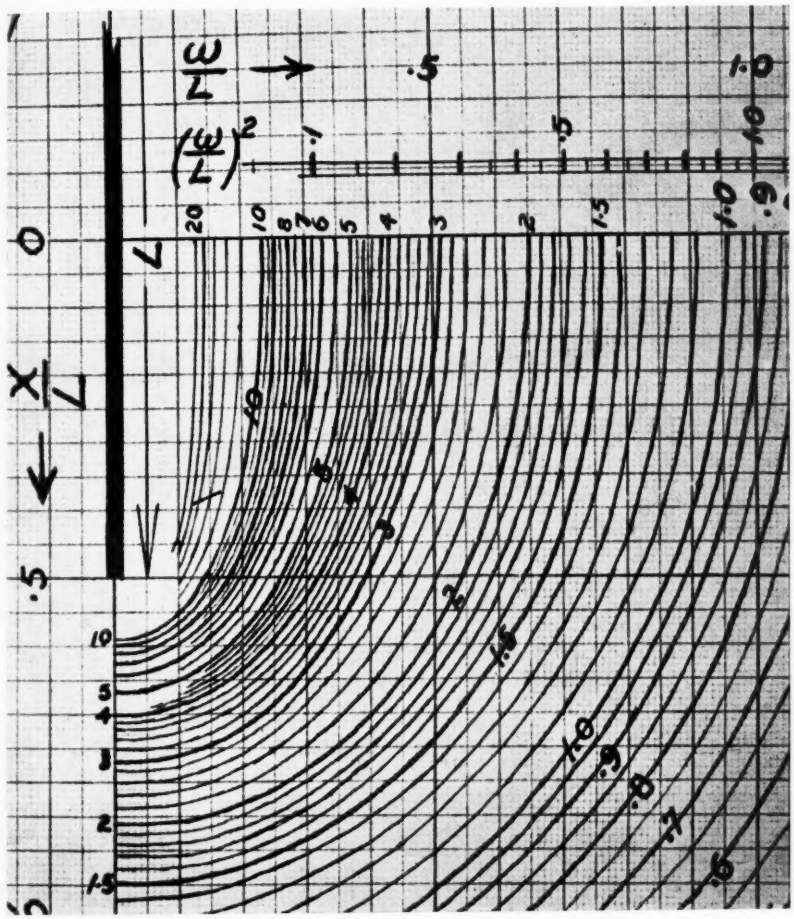

Fig. 3.

Similarly from Figure 4, $f_2 = 2.0$
Therefore,

$$R = 8.6 \frac{r}{\text{Imc.-hr.}} \times \frac{10\,\text{mgm.} \times 10\,\text{hours}}{1.5\,\text{cm.} \times 1.5\,\text{cm.}} \times 0.94 \times (1 - 2.0 \times (0.14/\text{mm.} \times 0.65\,\text{mm.} + 0.024/\text{cm.} \times 0.75\,\text{cm.})) = 282\,\text{roentgens.}$$

If several needles are present, the total dose is obtained by adding together the doses due to the needles individually.

PREPARATION OF DOSE CHARTS

A useful diagram of the distribution of dose near an arrangement of several needles unnecessary work can be avoided by suitable choice of points, by systematic arrangement of calculations, and by tabulating the results of each part of the calculation. Suggestions about how this may be done is the subject of this section.

The pattern of 14 needles shown in Figure 7 will serve as an illustration. It consists of 10 milligram needles, with 0.5 mm. walls of iridium platinum. The needles are spaced 1 cm. apart in two rows. The two rows are separated 4 cm. between

centers. The active length of the needle (length of the radium core) is 3.0 centimeters. The over-all length is 4.2 cm., but this fact is irrelevant.

Nine points, marked *a*, *b*, *c*, and *d*, are chosen in the plane of the needles. The dose is determined at nine depths below each point; 0.6 cm., 1.2 cm., 1.8 cm.,

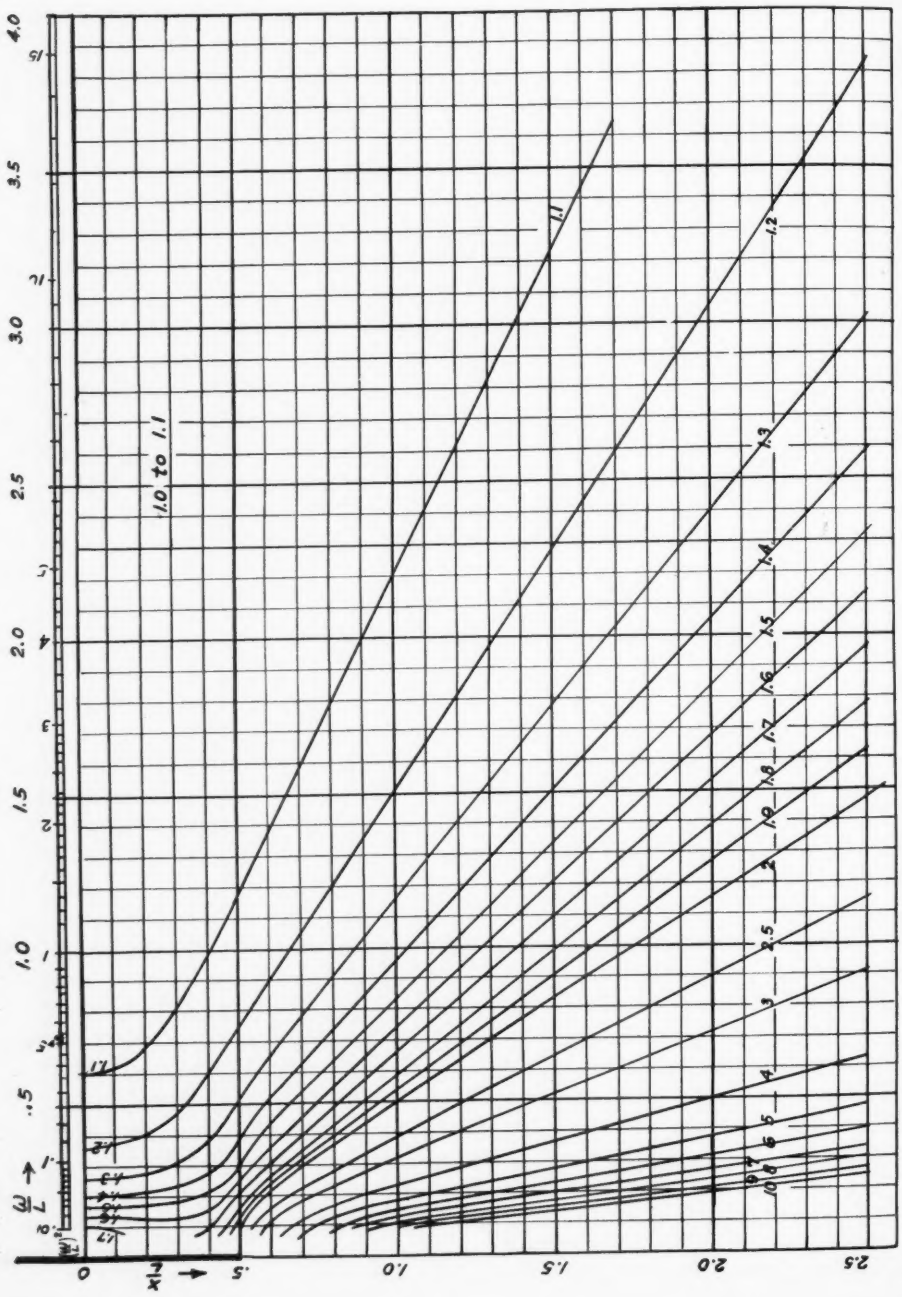

Fig. 4.

2.4 cm., 3.0 cm., 3.6 cm., 4.5 cm., and 6.0 cm., that is, at 81 points in all (Fig. 10). Since the corresponding points under the four d's are alike, and this is true also of the

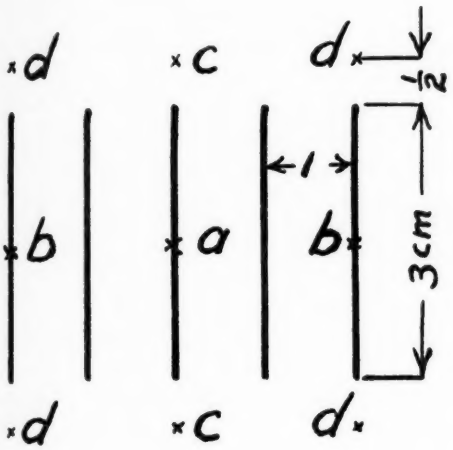

Fig. 5.

two b's and two c's, the number of values to be calculated is reduced to 36.

Figure 10 illustrates one kind of dose chart. In it are represented values of the dose at points under one each of the d's, b's, c's, and a. Other types of dose chart may be suggested; for example, a suitable vertical plane may be chosen such as through *cac* or through *bab*. A set of equal dose (isodose) curves may be drawn in freehand with tolerable accuracy, using the 81 points for guidance. Examples of charts of this kind may be found in some of the papers already cited.

It may be observed that at points under b and a the value of x is 2 cm. for every needle. The positions of d and c were chosen so that x is again 2 cm. for the nearest row of needles. Therefore, the effect of the upper row of needles on the point at a particular depth below b' is equal to its effect on the point at the same depth under d. Similarly the positions a, b', c', and d' are such that at a given depth below these four points, effects of the upper left-hand needles are equal. Thus by a suitable choice of points the amount of calculation has been reduced to a little more than a quarter of what it would otherwise be.

It is convenient to proceed in the follow-

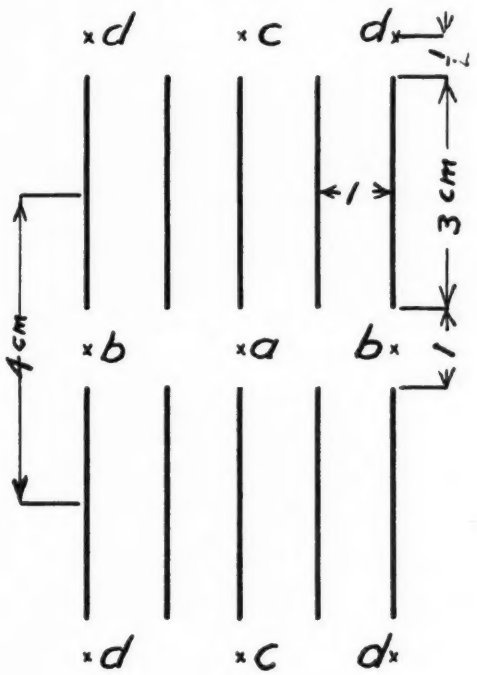

Fig. 6.

ing manner. One depth (*e.g.*, 0.6 cm.) is considered at a time. The dose at this depth under d is derived first. If the needles are alike, the first part of the formula, $\frac{MT}{L^2}$ is common to all of them. Multiplication by this factor can be postponed until the values for the rest of the formula, $(1-f_2(ks + k_1w))$, have been calculated for each needle and added together. As $(1-f_2(ks + k_1w))$ is evaluated for each needle it is carefully noted in a little table with a space for each needle.

The dose at the same depth under b is found now by adding up the appropriate values of $(1-f_2(ks + k_1w))$ and multiplying the sum by $\frac{MT}{L^2}$. These values of $(1-f_2(ks + k_1w))$ do not have to be calcu-

lated. They can be found in the table already prepared for the point under a, because every needle has the same position

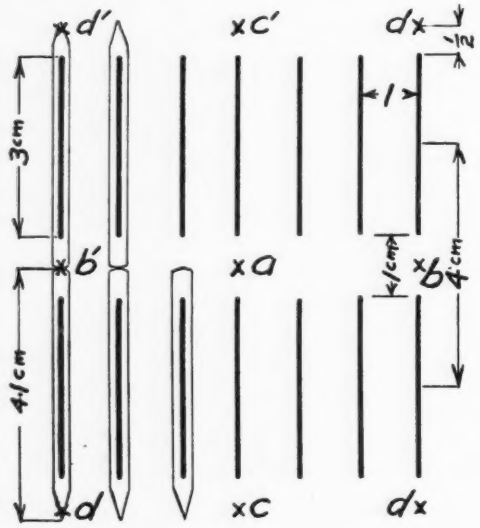

Fig. 7.

relative to the point under b, as some needle had to the point under a. This is true also for c and d.

Having completed one chart it is very easy to construct another chart for a smaller number of needles of the same design and spaced by the same intervals. The necessary values of $(1 - f_2(ks + k_1 w))$ are already available in the tables prepared during the calculation of the first chart. On the other hand, if the number of needles is increased $(1 - f_2(ks + k_1 w))$ must be calculated for the extra needles only.

The most tedious part of the calculations is the evaluation of $(1 - f_2(ks + k_1 w))$ for each needle. w, which is required to obtain f and f_2, is most easily determined by actual measurement on a drawing to scale. If this drawing is an elevation perpendicular to the axes of the needles, and of such a scale that L is represented by 1 cm., then w is given directly by the distance from needle to point, measured in centimeters by a centimeter scale. Graph paper is convenient for making drawings of this kind to scale.

The accuracy of these charts is sufficient for therapeutic purposes. Great accuracy offers no advantages in radium therapy because

(1) it is not possible to measure distances in tissue accurately,
(2) the boundary of a tumor is not sharply defined, and
(3) there are biological variables which cannot be controlled as accurately.

At points within 0.5 cm. of the needle axis, the method is inaccurate. This is due in part to the effects of beta rays from the metal walls of the needles. The dose so close to the needle is of little interest and must be interpreted cautiously, because very little is known about the extent to which the individual cell is influenced by effects on neighboring tissue, a question of great importance when the gradient of the ionization intensity is large.

It has been assumed in the derivation of the formulæ that practically no beta rays from the walls of the needle reach the point P. This is assured if at least 5 mm. thickness of flesh, wood, wax, rubber (lead-free), or similar material lies between the needle and the point. Hence if the radium needles are applied externally, the charts will give the dose on the *surface* of the skin only if a layer 5 mm. thick of such material is placed between the skin and the needles. The absorption in this layer is small and may be ignored. This layer has the additional advantage of reducing the skin dose necessary for a given tissue dose.

The dose due to a needle becomes inaccurate also when either f_2 exceeds 10 or $f_2 ks$ exceeds 0.4. This is due partly to the absorption in the ends of the needle and partly to mathematical approximations in deriving the formula. It sometimes occurs in computing charts for a combination of several needles. Although the calculated effect of the particular needle is inaccurate, the error is a very small part of the combined effect of all needles and, therefore, the accuracy of the chart is little affected.

Occasion may arise for using needles differing somewhat in design from these for

which the chart is intended. It is important, therefore, to know how much change in needle design may be permitted without producing excessively large differences in the actual dose from values indicated in the chart.

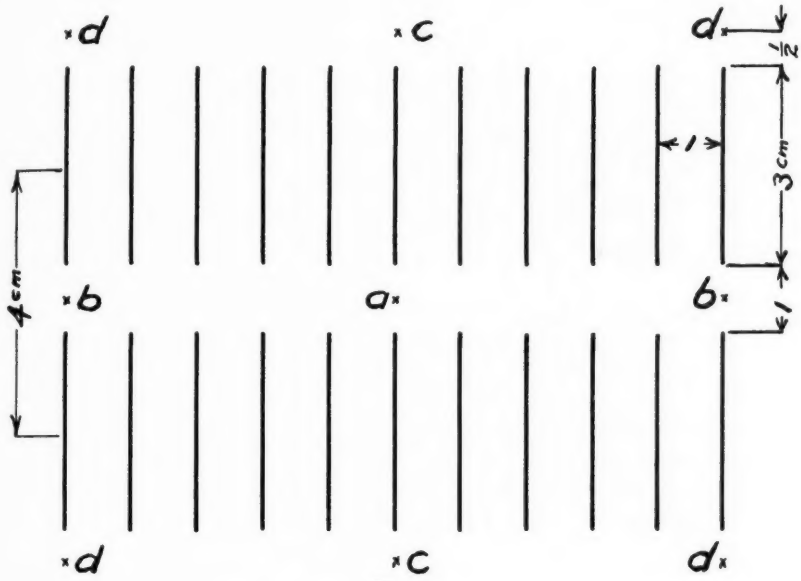

Fig. 8.

A change in M, the amount of radium in every needle, or T, the time of exposure, offers no difficulty. The dose is altered in proportion to the change in M and T.

A change in L or sk produces a change in the dose which depends on the position of the point. The following general statements indicate approximately the size of these changes. (A tolerance of 10 per cent is assumed for purposes of illustration only.)

In combinations of needles similar to the one described, that is, a number of needles all in one plane and equally spaced in parallel rows, the following empirical rule is a rough indication in the permissible change in L such that the dose at a point is not altered by more than 10 per cent: The distance of the point from the nearest end of the active length of the nearest needle should be measured. The change in L must not be great enough to alter this distance by more than 10 per cent. It should be noticed that this criterion permits very little change in L for points near the end of a needle, but permits quite large changes in L for points some distance away.

The values of the dose can be partly corrected for a change in sk by dividing them by $(1 - sk)$ and multiplying by $(1 - s'k')$ where sk and $s'k'$ are characteristic, respectively, of the needles of the chart, and the new needles. When thus corrected, the dose may be considered to be in error by less than 10 per cent if the value of $(1 - f_2 sk)$ at the point for the nearest needle to it has not been altered by more than 20 per cent. It follows that very little change in sk is permissible at points situated beyond the ends of the nearest needles in direction at small angles from their axes.

If the inactive ends of the needles are long, it may be desirable to overlap slightly the ends of needles in different rows to avoid a large inactive gap between rows. This involves placing the needles in an oblique position by rotating them slightly about their center, but does not introduce

objectionable error at depths greater than three times the diameter of the needles.

If the surface containing the needles is curved slightly (*e.g.*, in superficial application to the breast) dosage on the concave

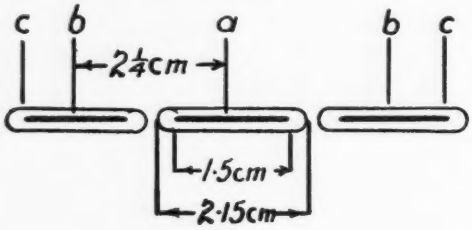

Fig. 9.

side is slightly increased. The increase is negligibly small at depths less than 2 or 3 cm. unless the curvature is very pronounced.

The following diagrams and tables apply to needles containing 10 mgm. radium, outside diameter 2.5 mm., wall of iridio-platinum 0.5 mm. thick, effective length (L) 3 centimeters. They are placed 1 cm. apart in rows separated 4 cm. between centers. The figures in the tables are the doses resulting one hour at various depths below the designated point on the diagram. The lines in the diagrams represent the cavities in the needles which contain the radium.

TABLE V.[3]—DOSE IN ROENTGENS IN ONE HOUR: 5 NEEDLES, 1 CM. APART, AS IN FIGURE 5; 10 MG. NEEDLES, ACTIVE LENGTH 3 CM., OUTSIDE DIAMETER 2.5 MM., WALL OF IRIDIO-PLATINUM 0.5 MM. THICK

mm.	a	b	c	d
6	220	174	82	64
12	116	88	60	47
18	70	55	44	35
24	47	37	33	26.4
30	32.5	26.7	24.6	20.6
36	23.6	20.2	19.0	16.5
45	15.7	13.7	13.4	11.8
60	9.0	8.2	8.0	7.3
75	5.7	5.4	5.3	5.0

Part II.—Imc.-hr. as the Unit of Dose

One milligram-hour per centimeter squared, abbreviated Imc.-hr., is the dose resulting in one hour from the gamma rays emitted by one milligram of radium at a point one centimeter from the radium. The size of this unit depends greatly on the nature of the radium container and the manner in which measurements are made. For example, if the walls of the radium container and the ionization chamber are very

[3] There are ten figures and six tables; the latter are numbered I, V, VI, VII, VIII, IX. Table V is so numbered because it refers to Figure 5; similarly for Tables VI to IX.

TABLE VI.—DOSE IN ROENTGENS IN ONE HOUR: 10 NEEDLES, 1 CM. APART, IN TWO ROWS, 4 CM. BETWEEN CENTERS, AS IN FIGURE 6; 10 MG. NEEDLES, ACTIVE LENGTH 3 CM., OUTSIDE DIAMETER 2.5 MM., WALL OF IRIDIO-PLATINUM 0.5 MM. THICK

mm.	a	b	c	d
6	165	128	90	71
12	120	94	68	55
18	88	70	62	43
24	64	53	40	34
30	49	41	32	27.4
36	38	33	25.5	22.5
45	26.7	23.5	19.0	16.9
60	16.0	14.6	12.4	11.6
75	10.5	9.9	8.6	8.3

TABLE VII.—DOSE IN ROENTGENS IN ONE HOUR: 14 NEEDLES, 1 CM. APART, AS IN FIGURE 7; 10 MG. NEEDLES, ACTIVE LENGTH 3 CM., OUTSIDE DIAMETER 2.5 MM., WALL OF IRIDIO-PLATINUM 0.5 MM. THICK

mm.	a	b	c	d
6	186	136	104	72
12	139	102	82	61
18	105	78	64	48
24	79	60	50	39
30	62	47	40	32
36	49	39	33	27.0
45	35	28.1	25.0	20.6
60	21.2	18.2	17.0	14.8
75	14.3	12.7	11.8	10.7

TABLE VIII.—DOSE IN ROENTGENS IN ONE HOUR: 22 NEEDLES, 1 CM. APART, AS IN FIGURE 8; 10 MG. NEEDLES, ACTIVE LENGTH OF 3 CM., OUTSIDE DIAMETER 2.5 MM., WALL OF IRIDIO-PLATINUM 0.5 MM. THICK

mm.	a	b	c	d
6	209	143	121	83
12	161	108	96	66
18	126	84	78	54
24	98	66	64	44
30	78	54	53	37
36	64	45	45	32
45	47	34	35	25.5
60	30	22.6	24	18.5
75	20.5	16.4	17.3	14.0

TABLE IX.—DOSE IN ROENTGENS IN ONE HOUR: 3 TUBES IN LINE, 2.25 CM. APART, AS IN FIGURE 9; 10 MG. TUBES, ACTIVE LENGTH 1.5 CM., OUTSIDE DIAMETER 2.5 MM., WALL OF IRIDIO-PLATINUM 1.0 MM. THICK

mm.	a	b	c
6	169 r	160 r	100 r
12	65	57	43
18	37	32	25.1
24	24.8	20.5	17.2
30	17.7	14.9	12.7
36	13.2	11.3	9.7
45	9.0	7.9	6.9
60	5.3	4.7	4.3
75	3.2	3.0	2.8

thin, a unit is obtained which is several times larger than one based on measurements which exclude the effects of the very soft radiation. Therefore, it is necessary to give further details in the definition.

Kohlrausch has shown that the hard radiation from radium in equilibrium with its disintegration products may be considered to consist of three Groups, I, II, and III, of different absorption coefficients (2). All softer radiation may be included in a fourth Group, IV.

It is of considerable advantage to avoid the effects of Group IV in defining the unit, for reasons to be considered later. This, of course, would not be justified if it were not for the fact that the amount of Group IV in the radiation which has penetrated the walls of needles and tubes of ordinary design is practically negligible.

The Imc.-hr. is, therefore, defined as the dose resulting in one hour from the three Kohlrausch Components of quality only in the radiation emitted from one milligram of radium at a distance of one centimeter.

The unit is realized by measurements made under conditions in which Group IV, the primary beta rays, and the secondary beta rays from any material of high atomic number such as the needle wall, are excluded. The measurement is then corrected for distance from the source by the inverse square law, and for absorption of Groups I, II, and III in the walls of the radium standard and the ionization chamber. For this purpose an ionization chamber with an inner wall of 5 mm. aluminium and an outer wall of 0.5 mm. lead has been used. The outer wall eliminated Group IV and the inner wall eliminated the secondary beta rays from the outer wall. Measurements were made also in chambers of wide variety of materials to test the assumptions made in this work, and to obtain values of the absorption coefficients of various materials under various conditions.

There are two advantages in using only Groups I, II, and III and excluding Group IV:

(1) Measurements of absorption coefficients are independent of the nature of the material of the inner wall of the chamber, provided that it is of low atomic number, thick enough to exclude secondary beta rays from dense material outside, and correction is made for the absorption in the wall itself. This is important because the only experimental quantities which enter directly into the realization and use of the Imc.-hr. unit are absorption coefficients.

(2) The conversion of Imc.-hr. into roentgens is simplified, because the effects due to the walls of the chamber are equal to the effects which would be produced by a large surrounding body of air as required by the definition of the roentgen. This is discussed in more detail in the next section.

Although foreign to the subject of this paper, it is interesting also that the secondary physical effects in biological tissue are proportional to the dose in roentgens due to these three quality groups, regardless of their relative intensities.

These advantages result from the fact that the absorption of Groups I, II, and III in materials of low atomic number is due practically entirely to the Compton effect. This is explained as follows:[4]

Gray (3) has shown that the Compton effect with hard gamma rays is not appreciably affected by the forces binding electrons to atoms, and that the probability of

[4] To avoid much repetition in this chapter, "light material" will mean material of low atomic number only, and "hard gamma rays" will refer to the radiation of Groups I, II, and III only.

a Compton collision depends only on the electron density of the material, and is proportional to it.

The measurements of Madgwick (4) and others have shown that the decrease in energy per unit distance travelled by a fast

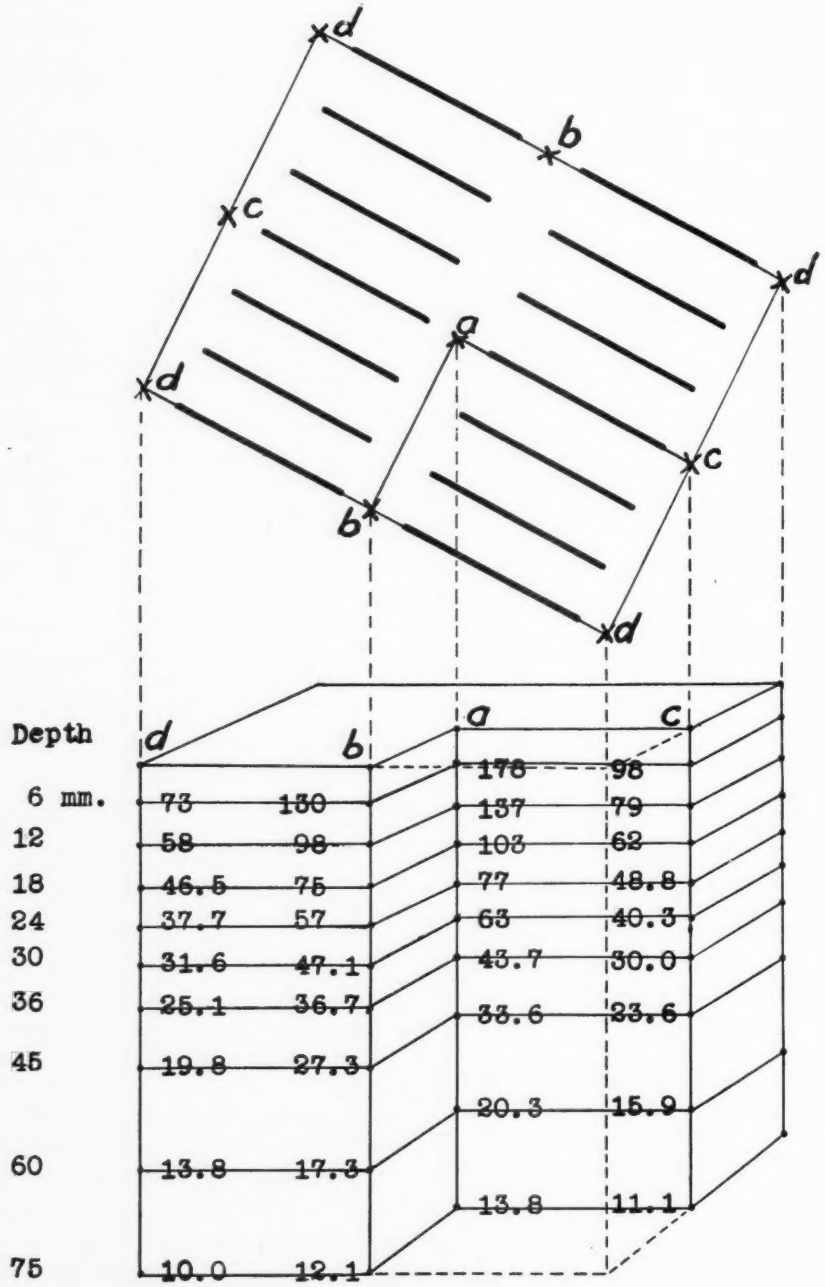

Fig. 10.

beta ray of a particular velocity is nearly proportional to the number of electrons per unit volume also. In the terminology of Bohr's theory of collisions (5), the rate of loss of energy depends on the average value for all electrons of the logarithms of their characteristic frequencies. This, however, appears to be nearly constant for different elements (6).

It follows that in light materials the product of the number of secondary beta rays and their true range is nearly constant. If these beta rays were straight (did not receive large angle deflections), it is evident that the number, velocity, and directional distribution of the beta rays crossing unit area of the boundary of such a material would be independent of the atomic number of the material, provided that the dimensions of the material are larger than the ranges of the beta rays in it. That is, the number, velocity, and direction of the beta rays from the walls of an ionization chamber would not depend on the material of the wall if it were free from elements of large atomic number.

The large angle deflections in the paths of the beta rays are chiefly due to encounters with the nucleus and, therefore, vary rapidly in number with atomic number. Since these nuclear collisions absorb comparatively little energy from the beta ray, the number and velocity of the beta rays are practically unaltered but the directional distribution depends greatly on the atomic number of the substance. If a hole is made in a large volume of the substance, the number and velocity of the beta rays crossing unit volume in this empty space are independent of the material. The direction of the beta rays is greatly dependent on the material. Therefore, in a small ionization chamber the number of beta rays from any *one* wall of the chamber depends on the material, but the total number of beta rays from *all* walls does *not*. It follows that the ionization current in the chamber is independent of the nature of the walls if the following conditions are satisfied:

(1) Chamber dimensions are small compared with the distance to the radio-active source, and the absorption in the walls is small, so that the intensity of the radiation is practically the same in all walls.

(2) Wall thickness is greater than the ranges of most of the beta rays in the material.

(3) Chamber walls are made of matter of low atomic number.

(4) Groups I, II, and III only are present in the radiation and Group IV is excluded by filtration.

Accordingly, definitions of units and methods of measurement have been adopted which satisfy these four conditions and thereby lead to the two advantages mentioned earlier.

Experimental proof of these conclusions is given by the measurements of Kohlrausch and Schrödinger (7). They measured the ionization in the two halves of an ionization chamber subdivided symmetrically by a partition of the metal under investigation. They found that the contribution to the ionization in the air in the chamber from the two sides of the thick metal partition is independent of the material to within 2 per cent for a series extending from Al (At. No. 13) to Zn (At. No. 30). (Suitable correction for absorption in the metal was made, of course.) The contribution increases with metals heavier than Zn, as may be expected from the occurrence of photo-electrons.

While this indicates that the total contribution from *all* the walls of the chamber is independent of their material, the contribution from any *one* wall *does* depend on the material. Due to the large angle scattering, the contribution of the "far" wall increases and that of the "near" wall decreases with atomic number. Confusion of the effect of a single wall (or other surface) and of all the walls has led to unjustified criticism of this method of measuring gamma rays.

Unfortunately Kohlrausch and Schrödinger's tests did not include materials of atomic number less than 13. Extrapolation in that direction may be made fairly confidently, for the influence of nuclear

binding of the electrons decreases, and we may assume that materials of lower atomic number are even less dependent on wall material.[5]

THE MEASUREMENT OF GAMMA RAYS IN ROENTGENS

The number of roentgens produced by radium cannot be measured in an ordinary parallel plate x-ray ionization chamber because the range of many of the secondary beta rays greatly exceeds the dimensions of the chamber. It may be deduced from the formula of Klein and Nishina (8) and experimental data that nearly half of the beta rays have ranges distributed very gradually between 10 cm. and over 300 centimeters. Hence the ionization current in a parallel plate chamber of the usual type increases rapidly as the distance of the plates from the x-ray beam is increased to about 10 cm. and then changes much more slowly. This is deceptive in creating an erroneous impression that the number of particles of range greater than 10 cm. is relatively small. Mayneord and Roberts (9) point out that this effect is even more pronounced if the aperture defining the beam is close to the electrode system, on account of the angular distribution of the rays. Attempts to measure the number of roentgens with instruments of this type may be expected, for this reason, to give results which are too small (10).

In another method (11) an electroscope of very thin paper walls is used as the measuring device. The thin walls permit secondary beta rays from the surrounding air to enter the electroscope. The wall effect may be eliminated by varying the thickness of the wall and extrapolating to zero. The assumption, implicit in the method, that the intensity is uniform throughout the volume of air contributing the beta rays entering the chamber is only realized if the radium is at a distance from the electroscope which is great compared with the range of the beta rays. Otherwise, too small a result may be expected.

A third method involves the use of small thimble chambers of material of low atomic weight (thus yielding negligibly few photoelectrons). This method assumes that the wall contributes a number of beta rays equal to that which would be contributed by a large volume of air surrounding the test volume as required by the definition of the roentgen. It has been already pointed out in discussing the Imc.-hr. unit that the ionization due to beta rays from the walls is practically independent of this material for primary radiation consisting of the Kohlrausch Groups I, II, and III, provided that the chamber is small compared with the distance to the radium, and is of material of low atomic number. Therefore, we have adopted a value for the number of roentgens equivalent to one Imc.-hr. which is based on experimental determinations in which these experimental conditions have been fulfilled.

The following determinations appear to have satisfied these requirements. The values as given in the original papers applied to definitions of the Imc.-hr. which differed in general from the definition given in the previous section. The values given here have been adjusted to comply with the definition adopted in this paper.

Glasser and Mautz (12) 8.6 r/Imc.-hr.
Mayneord and Roberts (9) 8.9 r/Imc.-hr.
Sievert (13) 8.2 r/Imc.-hr.

Other determinations have been made, *e.g.*, by Reitz and L. H. Gray, which have not been included here because information on their experimental conditions is not available to us at the present time. However, they do not depart greatly from the above values.

The mean value of 8.6 roentgens per Imc.-hr. has been adopted.[6] It is prac-

[5] Further experimental confirmation obtained in this laboratory will be published shortly.

[6] The Imc.-hr. unit used in this paper is about 7 per cent larger than the units used by Sievert and Mayneord. At the time this paper was read the author attempted to take this difference into account by modifying his own definition by the introduction of a numerical constant. Consequently, a value of 8.0 for a ratio between the units was adopted on that oc-

tically a constant on account of the definition which has been chosen, provided that soft gamma rays and beta rays from the needle or massive material are filtered out. This condition is fulfilled if the needle wall thickness exceeds 0.3 mm. of platinum or the equivalent, and the point P is separated from the needle wall by more than 0.4 mm. of flesh, wood, or similar material.

DERIVATION OF FORMULÆ AND TABLES

Assume that the axis of the radium needle lies along the x-axis of a system of cartesian co-ordinates. The quantity of radium is uniformly distributed throughout the length of the needle cavity from $x = \frac{-L}{2}$ to $x = \frac{L}{2}$. The needle wall has an effective mean thickness (see below) s and the absorption coefficient is k. The absorption coefficient of flesh is k'. Dose is to be calculated at point $P(x_1, y_1, z_1)$ in a time T.

Assume that radium is concentrated as a line source of infinitesimal thickness along the needle axis. This assumption produces an error of less than 1 per cent if the distance of P from the needle axis is over four times the diameter of the needle cavity.

Ignore the absorption in the radium and inert packing. This is usually much less than 1 per cent.

Ignore "end-effects" in the needle wall, *i.e.*, regard it as an infinite hollow tube. This will only introduce appreciable error if P is situated beyond one end of the needle in a direction from the center, making a small angle with the axis.

The element of dose (in Imc.-hr.) at $P(x_1, y_1, z_1)$ in time T, due to an element of length of the radium source between x and $x + dx$, is

$$\alpha D = \left\{ \frac{MT}{L}\, dx/((x_1 - x)^2 + w^2) \right\} \exp \left\{ - \frac{(ks + k_1 w)}{w} ((x_1 - x)^2 + w^2)^{\frac{1}{2}} \right\}$$

where

$$w^2 = Y_1^2 + z_1^2$$

The exponential term on the right, which represents the absorption in the needle wall and flesh, may be replaced by the first two terms of the series expansion

$$1 - \frac{ks + k_1 w}{w} ((x_1 - x)^2 + w^2)^{\frac{1}{2}} + \text{etc.}$$

Error due to this approximation does not exceed 2 or 3 per cent with ordinary needles, except at points beyond the end at small angles from the needle axis, as in the case of end-effects.

Integration between $x = \frac{-L}{2}$ and $x = \frac{L}{2}$ yields for the total dose in Imc.-hr.: $D = \frac{MT}{L^2} f_1(1 - f_2(sk + wk_1))$ which may be expressed in roentgens by $R = 8.6D$ and wherein

$$f_1 = \frac{1}{\left(\frac{w}{L}\right)} \tan^{-1} \left\{ \frac{w}{L} \Big/ \left(\left(\frac{w}{L}\right)^2 + \left(\frac{x}{L}\right)^2 + \frac{1}{4} \right) \right\}$$

and

$$f_2 = \log_e \left\{ \left(\left(\frac{w}{L}\right)^2 - \left(\frac{x}{L}\right)^2 + \frac{1}{4} + \frac{w}{L} \right) \Big/ \left(\left(\frac{w}{L}\right)^2 - \left(\frac{x}{L}\right)^2 + \frac{1}{4} - \frac{w}{L} \right) \right\} \Big/ 2f_1 \left(\frac{w}{L}\right)$$

f_1 is plotted in Figure 1, in terms of $\frac{x}{L}$ and $\frac{w}{L}$. f_2 is given in Figure 2, also as a function of $\frac{x}{L}$ and $\frac{w}{L}$. Wk_1 is small and may be ignored for values of $w < 1$ cm.

At distances from the needle greater than $2L$, f_1 approaches $1/(w^2 + x^2)$ and f_2 approaches $(w^2 + x^2)^{\frac{1}{2}}/w$; and these approximations may be used in calculations for such points.

casion. However, since this modification of the unit was entirely arbitrary, it has been abandoned.

The average effective thickness of the needle wall is given by the formula

$$s = r_1 - \frac{8r_2}{3\pi} - \frac{1}{8}\frac{r_2^2}{r_1} - \text{etc.}$$

r_1 and r_2 are, respectively, the outer and inner radii of the wall. This was originally derived theoretically, but on rather questionable assumptions regarding scattering. The formula has been repeatedly tested by experiment, however, and found to be fairly accurate. Usually only the first two terms need be considered.

The absorption coefficient k must comply with the requirements set forth in the discussion of the Imc.-hr. unit. Therefore it is determined experimentally under the conditions specified in that discussion (relating to ionization chamber design, filtration, etc.). For these measurements a glass-walled radium standard was inserted in metal tubes similar to the needle wall. Correction was made for the glass. k, a mean value for the three Kohlrausch Components, naturally changes slightly with the thickness of the material penetrated, but this is unimportant in practice and a suitable intermediate value is chosen.

k is smaller than the weighted mean of the values of the *total* absorption coefficients published by Kohlrausch and Sievert because it includes only part of the Compton absorption. This is due to the scattering in the needle wall. In materials of low atomic number the effective value of k for a needle wall is about 25 per cent of the total absorption. In heavier materials, the Compton absorption is less important and k increases to 80 per cent of the total absorption in the case of lead. The absorption in the wall of the ionization chamber is also affected by scattering and has been determined experimentally. The effective absorption coefficients for chamber walls of any material and for needle walls of the same material are found to be approximately equal.

The assumptions and approximations which have been made in deriving the formulæ do not produce large error except within 5 mm. of the needle wall and at points beyond the ends of the needle in directions from the center making angles of less than 15° with the axis. It was pointed out in Part I that this is not a serious limitation.

These claims have been tested by comparing values of the dose calculated by the present method with experimental values obtained by other writers with miniature ionization chambers, and by experimental tests of the variation of dosage at oblique angles carried out with larger ionization chambers.

SUMMARY

Part I.—Formulæ and tables are given for the calculation of the dose at a point near a radium needle or tube. The preparation of dose charts for combinations of several needles is described.

Part II.—Two units of gamma ray dose used in Part I are discussed, the milligram-hour per centimeter squared (Imc.-hr.) and the roentgen (r).

The derivation of the formulæ and tables used in Part I is given. The effective absorption coefficients employed were measured under certain experimental conditions which are specified. These differ greatly from total absorption coefficients which are not applicable in calculating dose.

The paper is an effort to simplify the calculation of the dose near radium needles by avoiding attempts to attain considerably greater accuracy than is required in radiological practice.

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THE DISTRIBUTION OF ROENTGEN RADIATION WITHIN THE AVERAGE FEMALE PELVIS FOR DIFFERENT PHYSICAL FACTORS OF IRRADIATION[1]

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IN the radiation treatment of carcinoma of the uterine cervix, a sufficient dose must be delivered not only to the primary lesion, but to the parametrial regions as well. Healy (1) has repeatedly stressed the fact that when radium is applied to the cervix alone it can be relied upon to control the disease directly in and about the primary lesion, but that it is incapable of destroying the tumor more than 3 or perhaps 4 cm. from the cervical canal. Some other means must be employed in an attempt to deliver a lethal dose of radiation to the outlying tumor-bearing regions. External irradiation with roentgen rays is the method used most commonly for this purpose, and it is rapidly assuming a greater importance in the treatment of cervical cancer. In many clinics particular schemes for the administration of pelvic irradiation have been developed, to increase the dose delivered to the tumor, and to improve the distribution of radiation throughout the pelvis. Further advancement in the treatment of cervical cancer seems to be promised by the development of better methods for the use of x-rays, in order to deliver a sufficient dose to the inevitable parametrial metastases, rather than by changes in the methods of applying radium to the cervix.

The amount of radiation that may be delivered to a tumor is limited by the reaction of normal tissues, and is also influenced by the location of the newgrowth and the body contour at its level. Studies upon the effect of different physical factors of the roentgen-ray set-up on the amount and the distribution of the radiation delivered within the pelvis are important for determining a method best suited for the treatment of cervical cancer.

The earliest detailed work upon the distribution of roentgen radiation within a medium was done by Kroenig and Friedrich (2). Measurements were made with an ionization chamber placed at various depths in a water phantom. The effects of different physical factors on the depth dose were studied. Shortly after the appearance of this comprehensive work, Dessauer and co-workers (3, 4, and 5) published an extensive study showing the distribution of radiation in a water phantom, for beams of radiation with various fields, voltages, and filtrations, as determined by photographic methods. They also prepared diagrams to illustrate the total dose obtained from radiation delivered through several portals into a given volume. Because of the short target-phantom distance used (25 to 30 cm.), the charts have little practical application at the present time.

Holfelder (6 and 7) prepared colored depth dose charts made of transparent material to represent the distribution of radiation in a beam of x-rays, shaded according to the relative intensities at different depths. He illustrated visually that a larger depth dose could be delivered at a given point within the body by increasing the number of ports, with all the beams directed toward the same region. Jüngling (8) and Bachem (9) have made similar studies.

In this country, Pfahler (10) made use of Holfelder's colored depth dose charts in the treatment of carcinoma of the cervix. He considered it desirable to deliver 120 per cent of an erythema dose to the tumor area by roentgen radiation. In the ordinary patient he was unable to obtain this dose in the mid-pelvis through single anterior and posterior fields, but found that it could usually be accomplished by increasing the number of ports. He empha-

[1] Presented before the Radiological Society of North America, at the Twentieth Annual Meeting, at Memphis, Tenn., Dec. 3–7, 1934.

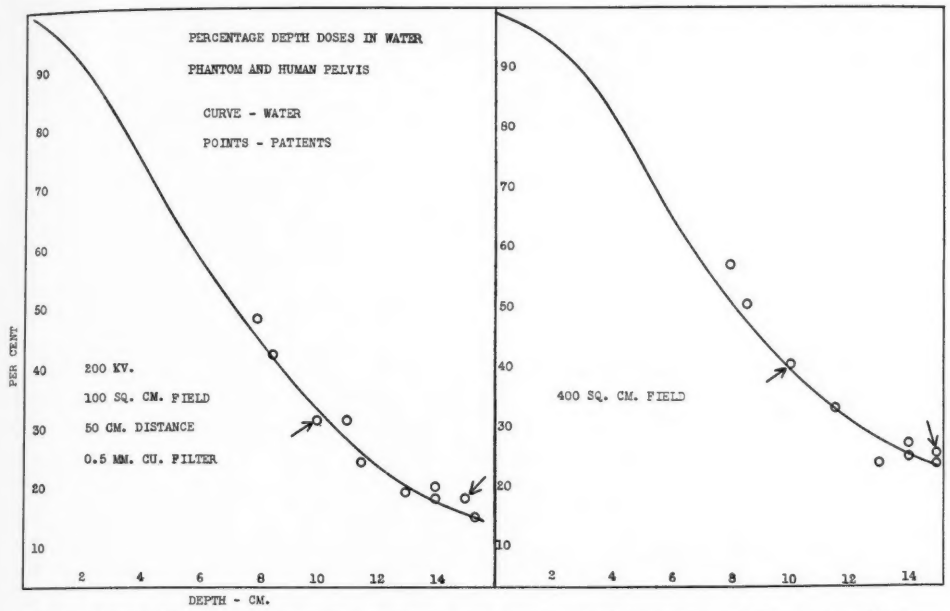

Fig. 1. Depth doses in human pelvis, compared with water phantom values. Curve, water phantom; points, patients (ionization chamber in vagina). Points indicated by arrows were measured with beam incident on posterior surface of body, all others with beam incident on anterior surface.

sized the caution that must be exercised to guard against delivering excessive doses to normal tissues when several fields are used.

Failla and Quimby (11) have published depth dose charts for varied dosage factors, showing the distribution of radiation within and outside the geometric beam. They obtained the experimental data by measuring depth doses in a water phantom with an ionization chamber similar to that described by Friedrich. Their tables show how the amount of radiation delivered at a specified depth is influenced by the target-skin distance, size of port, and filtration.

Failla (12) has described an objective method for the accurate administration of roentgen rays to each individual patient. The position of the tumor is indicated upon a diagram representing the measured body contour at the level of the neoplasm. This is superimposed over charts illustrating the distribution of specified beams of roentgen radiation. A proper technic is then worked out to attain a maximum depth dose in the desired area, with a minimum exposure of normal tissues.

Weatherwax and co-workers (13, 14, and 15) have followed the method described by Failla to deliver a predetermined dose of radiation to each patient. In the treatment of carcinoma of the cervix, from 120 to 130 per cent of an erythema dose can be delivered to the mid-pelvis by the use of his four-field technic.

In a report on the treatment of cervical carcinoma, Schmitz (16) has published charts showing about 90 per cent of an erythema dose delivered to the cervix by roentgen irradiation through single ports on the anterior and posterior pelvic surfaces. Healy (17 and 18) has published anatomical cross-section charts in the sagittal and transverse planes of the pelvis, showing the percentage distribution of x-rays. Radiation delivered at a 50 cm. target-skin distance through four ports 15 by 15 cm., supplied 120 per cent of the skin dose to the cervical region. From 100 to 120 per cent was obtained through a fairly wide portion of the pelvis. He also expressed the distribution of radiation within an average female pelvis in terms of threshold ery-

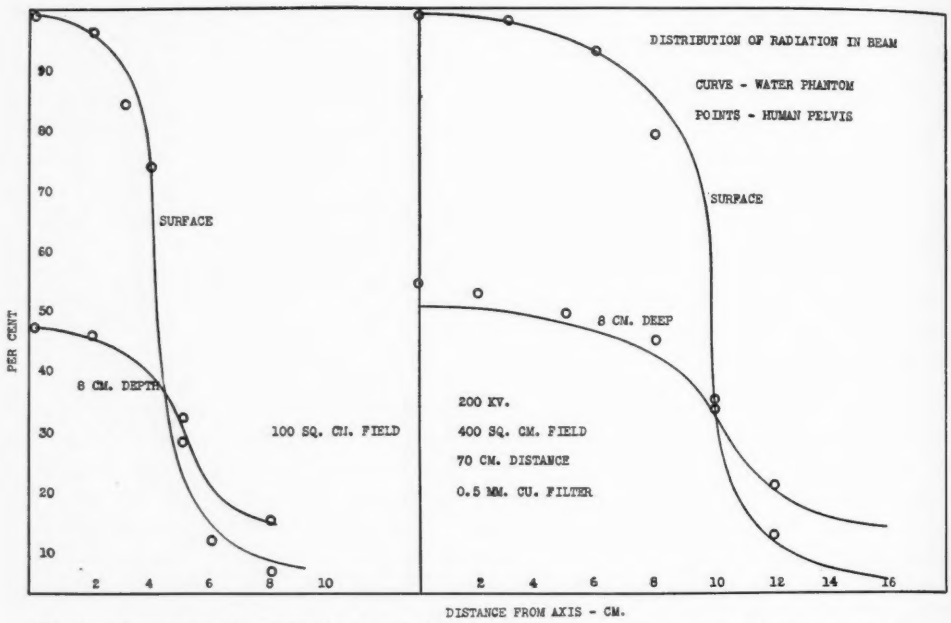

Fig. 2. Comparison of distribution of radiation throughout the beam in water phantom and in human pelvis. Curve, water phantom; points, patients.

thema doses from the combination of radium and roentgen-ray treatments.

All depth dose charts mentioned thus far have been obtained by measurements made in a water phantom. Quimby, Copeland, and Woods (19) compared the radiation at various depths in a human cadaver and in a water phantom, and found that, for points within the pelvis, the two were in close agreement. It was felt that the measurements in the cadaver should be supplemented by some made on living persons, and the present authors undertook a series of such measurements. The method and apparatus used are described in the paper just referred to; part of the results obtained were included therein. For each patient, the radiation was measured with the chamber on the surface of the body and in the vagina, the beam being centered over the chamber in each case. In all patients, measurements were made with beams incident on the anterior surface of the body; in a few, posterior irradiations were also measured. Fields of 100 sq. cm. and 400 sq. cm. were used, with x-rays at 200 K.V. peak, filtered by 0.5 mm. Cu and 2.5 mm. Al, and a target-skin distance of 50 centimeters. Obviously each patient could give a value for only one depth, that of the cervix. The use of patients of different sizes made possible the collection of values for depths ranging from 8 to 17 centimeters. The results obtained are shown in Figure 1, for fields of 100 and 400 square centimeters. The solid line in each case represents the water phantom values. The points indicate data obtained from individual patients, those marked with an arrow being measurements made with the beam incident posteriorly; all others were for anterior irradiations. It is evident from these curves that the water phantom data adequately represent the percentage depth doses delivered in the female pelvis for points at the center of the beam.

In the majority of pelvic irradiations, the beam is not centered over the cervix, but two anterior ports are used. In order to test the applicability of isodose charts from water phantom measurements, for points other than those on the axis of the beam, the chamber was left in place in the vagina while the x-ray tube was moved

varying distances to one side. A comparison of data thus obtained and of corresponding water phantom values is shown in Figure 2, for a depth of 8 cm., for a target-skin distance of 70 cm., and fields of 100 and 400 square centimeters. In each case the solid line represents the values of percentage depth dose in the water phantom for various distances from the axis. The crosses indicate individual observations on a single patient. The precision of measurement is not high; it is, however, evident that the water phantom charts represent satisfactorily the dose delivered within the pelvis.

It is evident from the above that numerous studies have been made upon the distribution of x-rays within the pelvis. Various authors have shown that the percentage depth dose can be increased by the use of higher voltages, heavier filters, longer distances, larger ports, or combinations of these factors. However, no correlated study has been published on the influence of varying specific factors on the distribution of radiation throughout the pelvis. The charts that have been presented to illustrate the advantages of different methods have dealt mainly with individual patients, and particular schemes of irradiation. It is impossible to obtain data for comparative values from a review of the literature, because of discrepancies in percentage values reported by various authors, even when they apparently used identical methods of irradiation and measurement. These variations are largely due to the different sizes of pelves considered in the individual cases.

For a practical comparison of methods of pelvic irradiation it is necessary to establish a certain body contour as a standard size, and then study the variations of distribution of radiation within this as various factors are changed, one at a time. The size of the pelvis to be used was determined from measurements made upon 25 women taken at random from the gynecological out-patient department. Anteroposterior diameters measured with the patient lying on her back in the usual position for treatment were found to vary from 15 to 31 centimeters. Lateral diameters taken in the same position ranged from 28 to 43 cm., and with the patient lying on her side varied from 27 to 38 centimeters. These measurements were made in a plane passing through the head of the femur and the upper border of the symphysis pubis. This level was chosen to represent approximately that of the cervix. The average anteroposterior and lateral diameters were 23 cm. and 35 cm., respectively. A diagram of the body contour at the level of the cervix was drawn with these dimensions.

Having adopted a pelvis of this size, the volume throughout which the distribution of radiation is to be studied is standardized. It is equally necessary to choose skin fields of a size suitable for the roentgen treatment of cervical cancer. Also, for comparing different methods of treatment it is desirable to keep the total area of irradiated skin constant on each of the pelvic surfaces, regardless of the number of fields used. That is, the total area of two small fields on the anterior or posterior pelvic surfaces should be the same as for one large port on the same region. If the same area, or the same volume, is irradiated in two given schemes, the systemic effect of the irradiation and the effect on normal structures may be considered the same, and a comparison made strictly on the basis of the radiation delivered to the involved region.

In general, the irradiated area should include the lower pelvic lymphatics as well as the promontory of the sacrum. Metastases from cervical cancer may go downward along the vaginal tube, but more frequently involve the lymph nodes at the pelvic brim, where the ureters may become obstructed. If there is no evidence of disease about the vaginal outlet, the direct beam should not be permitted to strike the external genitalia, because of the severe reactions which may be produced on the vulva. In order to avoid unnecessary exposure of sensitive tissues, and to include all of the tumor-bearing regions, the skin fields on most patients should extend from the middle of the symphysis pubis to the

iliac crests. Fields with a longitudinal diameter of 15 cm. will usually cover these bony landmarks. The transverse diameter of the irradiated skin area on the anterior and posterior pelvic surfaces should be about 20 centimeters. Therefore, a large field measuring 15 × 20 cm., or two smaller fields, measuring 15 × 10 cm. on each of these surfaces, seem to be desirable for the treatment of cervical cancer.

If lateral fields are to be employed, the same bony landmarks can be used that served to mark off the anterior and posterior areas. That is, the skin field can be placed so that it extends 15 cm. below the crest of the ilium. In most patients the lateral surface of the pelvis is sufficiently broad to permit the use of an area 10 cm. wide.

Depth dose charts were prepared according to the method described by Failla and Quimby (11) to illustrate the distribution within and outside the geometrical beam, for fields measuring 15 × 20 cm., and 15 × 10 centimeters. A mechanically rectified x-ray machine was used, with a filter of 0.5 mm. Cu and 2.5 mm. Al. Data were obtained for target-phantom distances of 50 and 70 centimeters.

With the standard size pelvis, the distribution of radiation was studied for a number of combinations of fields and distances, such as might be considered practical in the average radiological department. Diagrams illustrating the distribution were made by placing the proper depth dose chart in the correct position for treatment, under the outline of the pelvis drawn on transparent paper. The contribution from each beam was noted at various points within the pelvis, and the sum of all these was calculated for each point. Lines drawn through points receiving the same total radiation (so-called "isodose lines") divide the pelvis into regions receiving specified doses. Such lines were drawn for every 10 per cent variation in total depth dose.

The dose delivered on the skin by each beam was taken as 100 per cent. This does not indicate any definite quantity of radiation. Since the depth dose is expressed in terms of percentage of the quantity of radiation delivered at the surface of a single field, the per cent dose recorded in the diagrams represents the summation of the radiation reaching any given point after the sequence of treatments has been completed. If an erythema dose given to each of four ports delivers a depth dose of 80 per cent to the cervix, that region has received 0.8 of a skin erythema dose.

As stated above, variations of 10 per cent or more have been shown on the diagrams. In some instances, when all factors remained the same except that a greater target-skin distance was used, the depth dose delivered to a certain point shows no change on the diagrams, because the actual increase was less than 10 per cent. The values given in the diagrams have no relation to results previously published by other authors, nor do they express the exact percentage distribution of radiation within any particular individual treated with the same dosage factors. They represent the distribution within a pelvis measuring 23 cm. in the anteroposterior diameter, and 35 cm. in the transverse diameter. Patients of smaller dimensions will receive a greater percentage depth dose, and those of larger sizes will receive less. Since the size of the pelvis is kept the same throughout, the diagrams afford a comparison of the relative merits of the different methods of treatment.

Such a comparison should be based upon two factors: the amount of radiation reaching the tumor area, and the quantity delivered to normal tissues. In roentgen irradiation of the pelvis, the dose obtained at the cervix, or mid-pelvis, is usually considered of greatest importance. It should be borne in mind, however, that the outlying parametrial regions demand even greater consideration, because, in general, radium can be depended upon to control the primary lesion. In many cases the bladder and rectal regions are not infiltrated by the disease, and must be protected from excessive doses. A method of

external irradiation which will minimize the quantity reaching these normal, sensitive structures, and yet deliver a suitable depth dose to regions that may harbor disease, would be the most desirable.

One factor which will contribute to such a distribution is the directing of the roentgen-ray beams toward the parametria rather than toward the cervix. Such an arrangement has been used throughout the work reported here, whenever two fields were used on the anterior and posterior surfaces. These fields were spaced 2 cm. apart in the mid-line, to prevent overlapping of the radiation on the skin, and also to minimize the overlapping of the direct beams in the bladder and rectal regions. If the beams were tilted toward the mid-line so as to cross-fire on the cervix, a greater depth dose could be delivered to the primary lesion, but at the expense of the amount of radiation reaching the lateral portions of the parametria. Also, tilting the beams toward the mid-line increases the dose delivered to the bladder and rectum. Lateral beams add very little to the dose delivered to the cervix, bladder, or rectum. These were directed straight toward the mid-point of the anteroposterior diameter so as to deliver the maximum amount to the parametrium.

It should be noted that the data presented here pertain only to external irradiation. No consideration has been given to the uterine application of radium. The object of this work is to ascertain the most desirable method for the administration of roentgen radiation. In the publications of Healy and Schmitz already referred to are contained data upon the intravaginal and uterine applications of radium, which may be used in combination with any of the charts presented here.

SINGLE FIELDS 15 × 20 CM. ON THE ANTERIOR AND POSTERIOR PELVIC SURFACES

Due to the broad area on the anterior and posterior surfaces of the pelvis, single large fields have often been used in these regions for roentgen treatment of pelvic neoplasms. If large fields are employed, the beam of radiation can include the parametrial regions as well as the cervix. By the use of a few large fields, the pelvic cycle can be completed in a shorter time. An argument sometimes advanced for the use of large fields is the increased depth dose obtained with increased area. The corresponding argument for small fields is that the skin reaction in this case is less than with a larger area. These statements apply only to the use of single isolated fields; they would have to be considerably modified for the type of irradiation represented by the pelvic cycle. When the total irradiated area is the same, it makes little difference whether it is all exposed at once or at two separate sittings. Therefore the comparison of the two- and four-field technics on the basis of the distribution of radiation, as shown, does not have to be modified by these considerations.

The percentage distribution of radiation within the pelvis, for x-rays delivered through single fields measuring 15 × 20 cm. on the anterior and posterior pelvic surfaces is shown in Figure 3, for target-skin distances of 50 and 70 centimeters. At 50 cm. this two-field method delivers a depth dose of from 50 to 60 per cent at the mid-pelvis, or cervical region. The transverse diameter of the region receiving this dose, at the depth mentioned, is 11.5 centimeters. Both the bladder and rectum receive a greater dose (about 60 to 80 per cent). Throughout the parametria the minimum dose, distributed over a volume 17.5 cm. wide, is 40 per cent.

If the same dosage factors are used, except that the target-skin distance is increased to 70 cm., the percentage depth dose reaching the cervix is increased about 10 per cent. There is a corresponding rise in the dose delivered to the bladder and rectum. Throughout the parametria a minimum dose of 40 per cent is distributed over a volume 19 cm. wide.

In both of these methods of treatment the depth dose delivered to the cervix is considerably greater than that throughout most of the parametria. Also, the amount

of radiation reaching the bladder and rectum is from 20 to 30 per cent greater than the dose delivered to the primary lesion. To alter the method of treatment so that a greater percentage of the radiation would be delivered to the parametria, and to prevent such a wide discrepancy between the dose reaching the cervix and

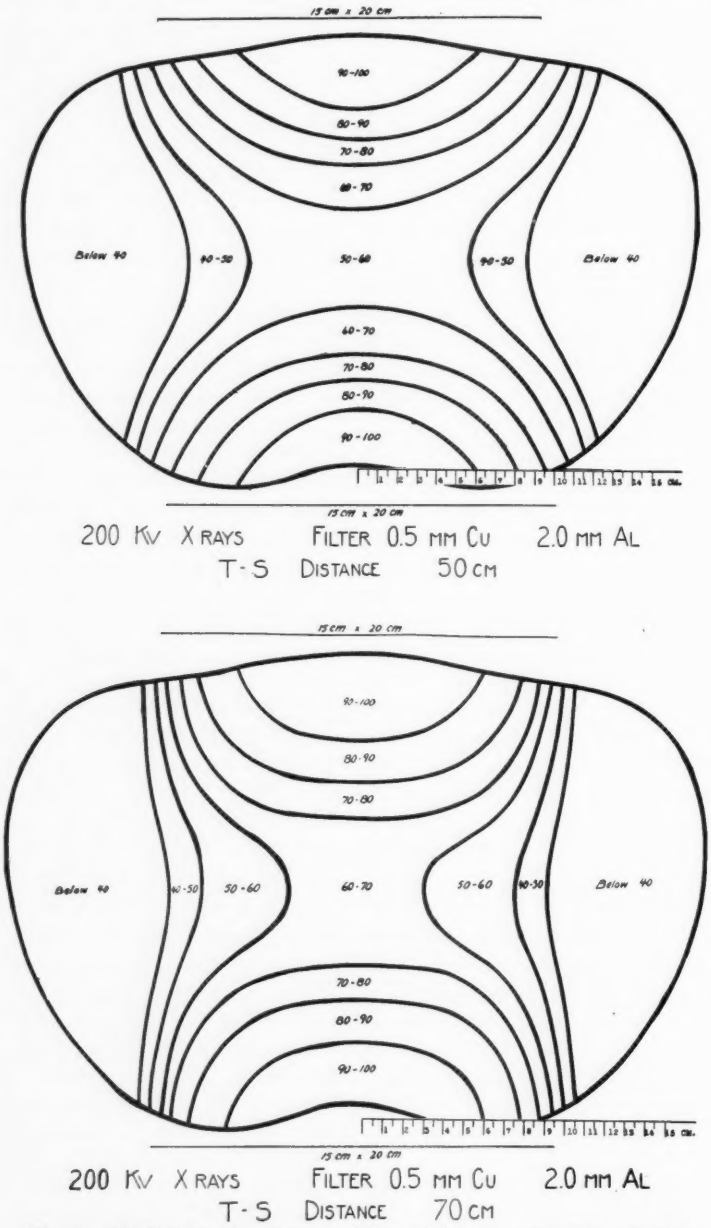

Fig. 3. Distribution of roentgen radiation within the average female pelvis for large single fields measuring 15 X 20 cm. on the anterior and posterior surfaces.

the bladder and rectal regions, would be a definite advantage.

TWO FIELDS OF 15 × 10 CM. EACH, ON THE ANTERIOR AND POSTERIOR PELVIC SURFACES

The percentage distribution within the pelvis, of radiation delivered through two fields measuring 15 by 10 cm. each, on both the anterior and posterior pelvic surfaces, is shown in Figure 4, for target-skin distances of 50 and 70 centimeters.

At a 50 cm. distance this method delivers a depth dose of from 60 to 70 per cent to the cervical region. Both the bladder and rectum receive the same dose as is delivered to the primary lesion. The total amount of radiation reaching the mid-pelvis is a slightly greater percentage of the skin dose than is obtained through large single fields on the same pelvic surfaces, when an identical target-skin distance is used. The distribution throughout the parametria is somewhat better with the four-field method. A minimum dose of 40 per cent is distributed over a wider volume (21 instead of 17.5 centimeters).

If four skin ports are used with a target-skin distance of 70 cm., a depth dose of from 60 to 70 per cent is delivered to the cervix, bladder, and rectum. Throughout the parametria the percentage depth dose distribution is similar to that obtained from a two-field method with the same target-skin distance, except that a minimum dose of 40 per cent is distributed over a volume 22 cm. wide. The dose recorded on the diagram for the cervix does not show an increase over that obtained in the same region by the four-field method at 50 cm. distance, or by large single fields at 70 cm., because the increase is less than 10 per cent. However, the diagram does illustrate that the lateral borders of the volume receiving from 60 to 70 per cent are pushed further out into the adjacent parametria.

The greatest advantage of the four-field method is the protection it gives to the bladder and rectum. These regions are spared doses in excess of the amount of radiation delivered to the cervix, when the beams are oriented as described above.

LATERAL FIELDS OF 15 × 10 CM. AND LARGE SINGLE FIELDS ON THE ANTERIOR AND POSTERIOR PELVIC SURFACES

If lateral beams are added to any anterior and posterior port arrangement, the depth dose delivered to the parametrial regions will be increased considerably. On the other hand, because of the depth of the cervix below the lateral skin surface, the increase in the dose reaching the primary lesion will be small. Such a distribution within the pelvis may be desirable, because the primary lesion can be treated by radium applied to the cervix. The effect of adding lateral beams to the port arrangements already discussed will now be considered. In each instance the lateral fields measured 15 × 10 cm., with the same target-skin distance as was used for the anterior and posterior fields. The percentage distribution for radiation within the pelvis, for x-rays delivered through lateral fields and large single fields on the anterior and posterior pelvic surfaces, is shown in Figure 5, for target-skin distances of 50 and 70 centimeters.

At a 50 cm. target-skin distance this method delivers a depth dose of 70 per cent to the cervix, and a surrounding region 8 cm. wide in the transverse diameter. Lateral to this region the total depth dose is increased as the skin surface is approached, so that the bulk of the parametrium receives from 70 to 90 per cent. The dose delivered to the bladder and rectal regions is also from 70 to 90 per cent each.

If the same port arrangement is used for a target-skin distance of 70 cm., the dose delivered to the cervix and surrounding tissues is increased to 80 per cent. The bulk of the parametria receives from 80 per cent to about 95 per cent, which is an increase over the dose delivered to the same regions by the preceding method. A somewhat greater dose is delivered to the bladder and rectum than to the cervix,

each receiving from 80 per cent to about 95 per cent.

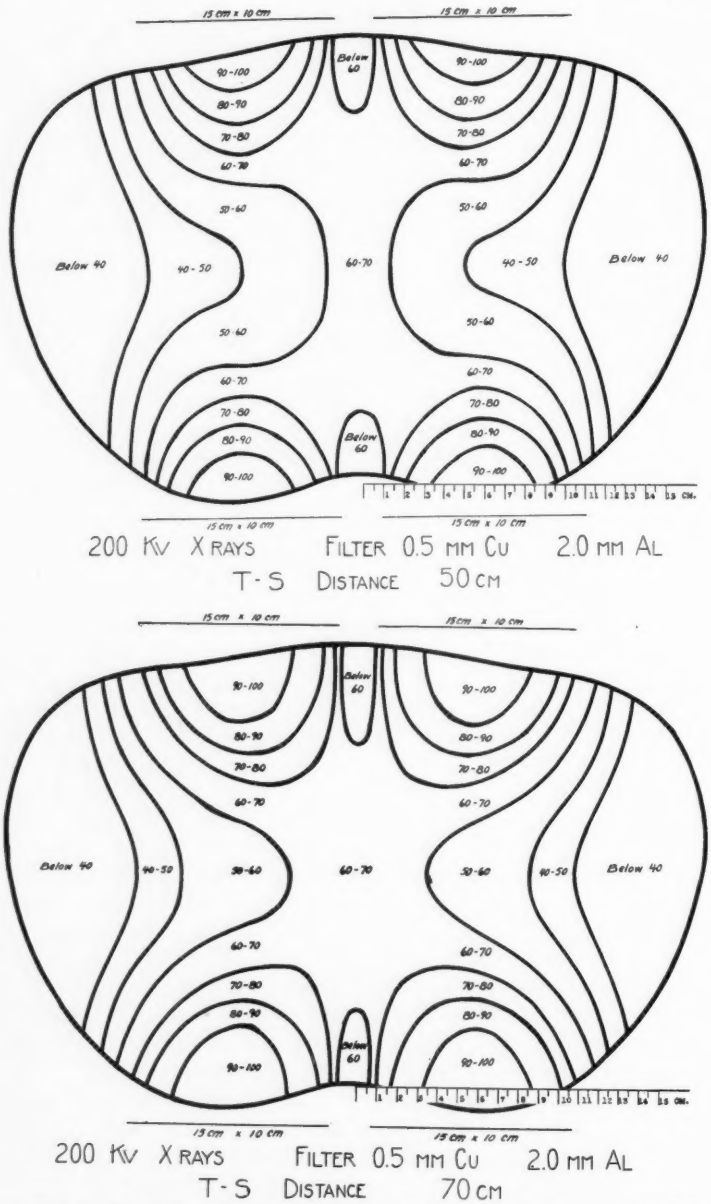

Fig. 4. Distribution of roentgen radiation within the average female pelvis for two fields measuring 15 × 10 cm. on both the anterior and posterior pelvic surfaces.

In these methods of treatment the lateral beams greatly increase the dose delivered to the parametria, and to a lesser extent the dose delivered to the cervix. In both methods the cervix dose is distributed over a volume of about 8 cm. wide, which would extend about 4 cm. on the right and left sides of the cervical

canal, and probably be within the volume that can be controlled by radium. Lateral

per cent greater than the dose delivered to the cervix.

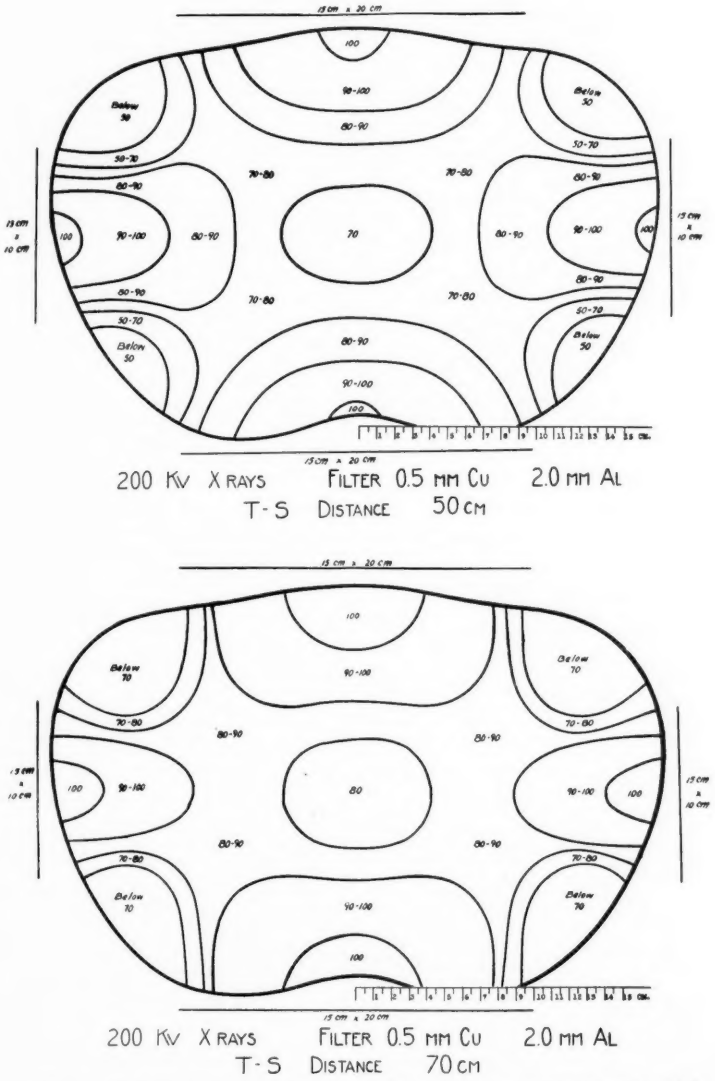

Fig. 5. Distribution of roentgen radiation within the average female pelvis for the addition of lateral beams to single large anterior and posterior portals.

to this dosage area, at distances beyond the zone of effect by radium applied to the cervix, the depth dose is considerably greater. However, the dose delivered to the bladder and rectum is from 18 to 27

LATERAL FIELDS OF 15 × 10 CM. AND TWO FIELDS ON BOTH THE ANTERIOR AND POSTERIOR PELVIC SURFACES

Diagrams illustrating the distribution of radiation within the pelvis for the addition

of lateral beams to the four-field set-ups already discussed, for target-skin distances of 50 and 70 cm. are shown in Figure 6.

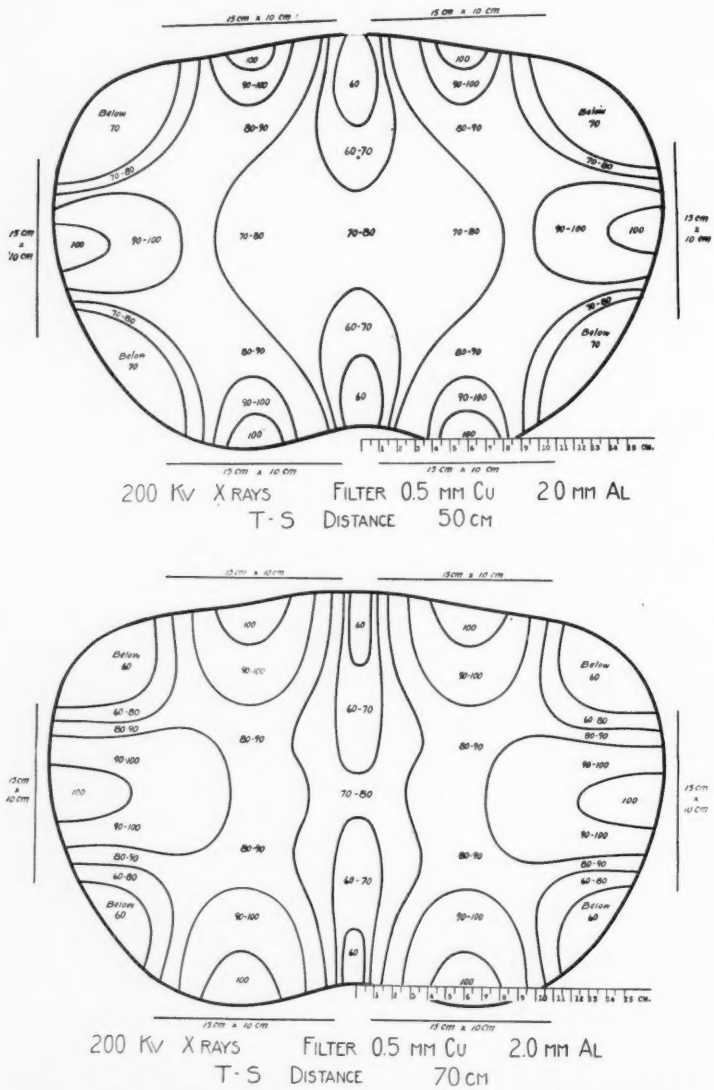

Fig. 6. Distribution of roentgen radiation within the average female pelvis for the addition of lateral beams to two portals on both the anterior and posterior pelvic surfaces.

If a 50 cm. target-skin distance is used for this six-field arrangement, the cervix receives a depth dose of from 70 to 80 per cent. The transverse diameter of this dosage area is 16 cm. wide. The distribution throughout regions lateral to the cervical canal is not very different from that obtained from lateral beams and large single anterior and posterior fields at a 50 cm. target-skin distance. However, in the six-field technic, both the bladder and rectum receive no more radiation, and probably less, than the cervix does.

If a 70 cm. target-skin distance is used, the cervix receives about 70 to 80 per

cent. The distribution throughout regions lateral to the cervical canal is not very different from that obtained in the same method employing large fields instead of double ones on the anterior and posterior surfaces. However, as has been noted for all double anterior and posterior port arrangements, the bladder and rectum receive no more radiation than the cervix does, and probably a little less.

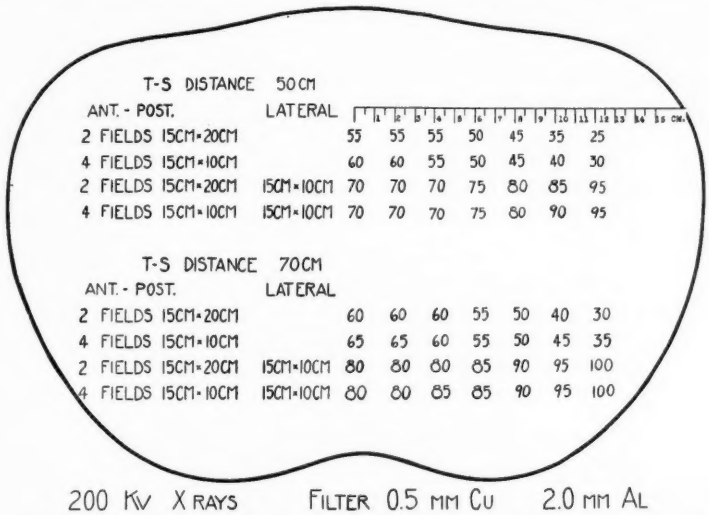

Fig. 7. Doses delivered to the mid-pelvis, and to points 2 cm. apart along a transverse line drawn directly lateral to the cervix, for each of the port arrangements and target-skin distances considered.

DISCUSSION

A study of the various charts illustrating the percentage distribution of radiation in the pelvis for different methods of external irradiation, reveals that certain procedures have definite advantages over others. The criteria by which the efficiency of any method may be judged in this manner are based upon physical expressions of the amount of radiation reaching any given point. There are two factors to be considered; first, the dose delivered to the mid-pelvis and to the parametrial regions, which represent the tumor area; and second, the ratio of the dose reaching the bladder and rectal regions to that obtained at the cervix.

The doses delivered to various points along a line drawn in the transverse diameter through the middle of the pelvis would indicate the minimum amounts of radiation delivered to the tumor-bearing region in patients with carcinoma of the cervix. The doses delivered to the middle of the pelvis, and for every 2 cm. lateral to this point for a distance of 12 cm., are shown within a diagram of the pelvis in Figure 7. Values are presented for all of the methods which have been discussed, and were taken from the original diagrams made in preparation of those given in this paper. The values represent the summation of radiation reaching specific points from all contributing beams. They follow closely, but not exactly, the percentage areas illustrating the distribution of radiation for specified dosage factors. Variations are due to the fact that the table shows differences of more than 5 per cent, whereas the zones on the diagrams are made by 10 per cent steps.

The distribution of radiation throughout the pelvis for the various sets of ports has already been discussed in detail. It has been shown that the use of large single fields on the anterior and posterior pelvic

Fig. 8. Distribution of radiation within the average female pelvis for two skin portals measuring 15 × 10 cm. each on the anterior pelvic surface.

surfaces delivers a greater dose to the bladder and rectal regions than to the cervix. It has also been shown that double small fields, half the size of the larger ones, can be used to irradiate an equal area of skin, to deliver the same depth dose, and to spare the bladder and rectum from doses in excess of that reaching the cervix. The addition of lateral fields to any port arrangement increases the depth dose delivered at all points within the pelvis. The greatest improvement is in the parametrial regions, which, at a distance of 6 cm. from the mid-line, receive more radiation than the cervix. In view of these facts it seems that a six-port arrangement (two anterior, two posterior, and one on each lateral surface), with a 70 cm. target-skin distance, is the best of the methods here investigated for delivering roentgen radiation to patients with cervical cancer.

No set rules can be established for the treatment of all patients. However, in most cases it is possible to irradiate all of the tumor-bearing region by the six-field technic just described. If the fields are 15 cm. long, they will usually reach from the middle of the symphysis pubis to the iliac crests, which can be used as bony landmarks for outlining the portals around the pelvis. A radiograph is shown in Figure 8 to illustrate the distribution of radiation for the two anterior fields. For the preparation of this film, the vaginal vault was first marked by an opaque contrast ma-

terial in order to locate the position of the cervix. An exposure was made with the patient lying on her back, and the tube centered in the mid-line, with a target-skin distance of 70 cm., over a point halfway between the middle of the symphysis pubis and the iliac crests. The tube was then centered over the left pelvis in the usual manner for treatment. Without disturbing either the patient or the cassette containing the film, a lead shield with an open port measuring 15 by 10 cm. was placed over the abdomen so as to confine the beam to the left anterior pelvis in the correct position for treatment. A second exposure (150 per cent of the first) was then made. The same process was repeated on the right side. The positions of the two fields can be clearly seen on the radiograph. From the contrast material in the vaginal vault it can be seen that the cervix as well as the promontory of the sacrum is included in the direct beams. There is slight overlapping of the two beams on the film; they probably come together at about the depth of the cervix. As has been stated before, heavy roentgen irradiation of the cervix is not felt to be absolutely necessary, since radium can be used to deliver sufficient radiation to this region. It seems more logical to separate the fields in the mid-line in order to protect the bladder and rectum from excessive doses. A separation of about 2 cm. is preferable to greater or less spacing. If the fields are brought closer together, the dose delivered to the bladder and rectum is increased, and there is danger of overlapping the fields on the skin. If there is a separation of much more than 2 cm., the dose delivered to the mid-pelvis is apt to be decreased so that too little radiation will be delivered to the tissues located at a distance beyond the radius of action of radium applied to the cervix.

No statement has been made about the dose delivered to the skin, nor is it necessary to consider the rate at which radiation is administered in a study of its distribution throughout the pelvis. It is only necessary to deliver equal doses to all of the fields in order to obtain the percentage depth doses that have been given for certain specified conditions. As far as the ratio between surface and depth dose is concerned, it makes no difference whether the radiation is administered at a single sitting, or in several exposures. If a divided dose method is used, a greater total amount of radiation may be delivered to the skin, and the total depth dose increased in the same ratio.

As has been stated, all the data given thus far are for x-rays at 200 K.V. filtered by 0.5 mm. Cu and 2.5 mm. Al. Since in many clinics filters of 2 mm. Cu are in current use, it is of interest to know what increase in depth dose would be attained for the various schemes of irradiation, with this increase in filter. Quimby and Marinelli (20) have shown that, with a field of 100 sq. cm., increasing the filter from 0.55 mm. Cu to 2.16 mm. Cu increases the dose on the axis of the beam at 5 cm. depth by 3 per cent, at 10 cm. depth by 6 per cent, and at 15 cm. depth by 12 per cent. Failla and Quimby (11) have shown that the effect of change in filter is independent of the field and of the target-skin distance; therefore, the values just given apply to the irradiation systems discussed in the present paper. It is evident that the increase in depth dose throughout the pelvis, for the increase in filter under discussion, would be about 6 per cent. In order to obtain this slight increase in depth dose it is necessary to use an irradiation period three times as long, to compensate for the absorption in the filter. If the compound filter of Thoræus is used (to equal 2 mm. Cu), the irradiation time is twice as long as for 0.5 mm. Cu. An increase of the target-skin distance from 50 to 70 cm. produces twice as much improvement in depth dose as the increase in filter from 0.5 to 2.0 mm. Cu, and requires only half as much increase in time. From the economic point of view it is evident that increases in filtration are undesirable. The question of an improvement in results with the change in quality of radiation produced by the increase in

filter is as yet far from being satisfactorily answered.

With regard to the economic aspect, certain other considerations may be set forth. Increasing the target-skin distance from 50 to 70 cm. means that the time of irradiation must be doubled to deliver the same skin dose. Six fields require three times the treatment time of two, and once and a half the time of four. In some clinics, where pressure of work is so great that any improvement in technic must be weighed against the increased time required, an analysis should be made of the relative merits of various schemes. It is evident that of the schemes here considered the six-field technic with a 70 cm. target-skin distance is the most desirable. However, six fields at 50 cm. can be treated in half the time, and four at 70 cm. in two-thirds the time. Six fields at 50 cm. deliver a dose only slightly less along the mid-line than six at 70 cm., and the distribution throughout the parametria is almost as good. Hence by this means the time may be cut in two without severe loss of dosage. On the other hand, four fields at 70 cm. give smaller doses both in the midline and the parametria than six fields at 50 cm., although the treatment time is longer. In the same way any proposed technic may be compared with one chosen as standard, in order to determine its relative advantages and disadvantages.

The large fields were, of course, directed straight into the pelvis. When two fields were used on the anterior and the posterior surfaces, they were also directed straight into the pelvis, and separated in the midline by a distance of 2 centimeters. This was done in order to direct the radiation toward the underlying parametria, and to protect the bladder and rectal regions from doses in excess of the amount delivered to the cervix. For these reasons the use of two fields on both the anterior and the posterior pelvic surfaces is more advantageous than large single ones, which deliver a greater amount of radiation to the bladder and rectum than to the cervix. However, the distribution of radiation throughout the tumor-bearing region is not very different for the two methods when the total irradiated area and the target-skin distance are kept the same.

Lateral beams add slightly more to the cervix than to the bladder and rectal doses. The most marked benefit from such fields is obtained in the parametrial regions (beyond the radius of effect from radium applied to the cervix), which in this case receive a greater dose than the cervix itself. Therefore, the combination of lateral beams with two fields on both the anterior and posterior pelvic surfaces affords the best distribution of radiation throughout the pelvis. By this means the bladder and rectum receive no more, and probably less, radiation than the cervix does. Radium can be applied to the cervix, so that the primary lesion receives a greater dose than either the rectum or bladder. The greatest amount of roentgen radiation is delivered to the parametrial regions, which cannot be adequately treated by cervical application of radium.

SUMMARY AND CONCLUSIONS

The distribution of radiation throughout a pelvis of standard dimensions (determined from measurements upon 25 patients) has been studied for a variety of methods for the administration of roentgen radiation. By this means a comparison can be made of the relative effectiveness of the different methods studied. Patients of smaller size than the standard pelvis would receive a greater percentage depth dose than has been recorded on the diagrams; larger patients a smaller amount of radiation in the tumor-bearing region. The diagrams that have been presented serve to indicate which method is best suited for the treatment of carcinoma of the uterine cervix.

The different port arrangements which have been studied were as follows: large single fields on the anterior and the posterior pelvic surface; two fields on the anterior surface, with two on the posterior surface, and the combination of lateral

beams with each of the above plans. Each of the four different port arrangements was studied for target-skin distances of 50 and 70 centimeters. Large single fields on the anterior and posterior pelvic surfaces measured 15 cm. in the longitudinal diameter, and 20 cm. in the transverse. If two fields were used on these surfaces, they measured 15 × 10 centimeters. By this means the total irradiated area on these surfaces was kept the same. In those instances in which lateral beams were added, these fields were also 15 × 10 centimeters.

The percentage depth dose may be increased more economically by the use of greater target-skin distances than by the use of heavier filters.

A six-field technic (two anterior, two posterior, and one on each lateral surface), oriented in the manner described, with a target-skin distance of 70 cm., is the most desirable of the methods herein investigated for the treatment of cervical cancer.

In most cases the lower border of the fields should not extend below the middle of the symphysis pubis. The direct beam will then include the cervix and upper vagina, but will not strike the external genitalia. If the longitudinal diameter of the fields is 15 cm., the promontory of the sacrum will be included, and the skin portals will usually extend to the crest of the ilium. These two fixed levels (middle of the symphysis pubis and iliac crests) are advocated as bony landmarks for the marking out of pelvic fields.

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THE RELATION OF AIR IONIZATION TO RADIATION ABSORBED AND THE EFFECT ON BODY TISSUES[1]

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Professor of Radiology, New York Post-graduate Medical School and Hospital of Columbia University

AS Dr. Taylor has announced, this is a volunteer contribution to replace some of the absentees on the program. The detail of my subject matter is not at hand but in New York. The presentation is, therefore, extemporaneous, with a further apology for the hastily prepared slide of the chart. This difficulty will be remedied in the final publication.

Physicists have done much to give us standards of quantitative and qualitative measurements. There remains considerable doubt and controversy, with uncertainty in the linking of the physical dose measurement with observed skin reaction and biologic effect. Until some definite relation between physical quantitative and qualitative radiation measurements and skin and biological reaction is established present-day standardization remains but an arbitrary estimate of radiant energy or tube output.

For more than twenty years we have continued our study of these problems, and in an article published as early as 1920 (1) I recorded my impressions on the relation of skin and human tissue reaction to absorption as determined by photographic measurements.

With the improvement in ionometric quantitative dosimetry, this method became a supplement to and substitute for the photographic, pastille, and other dosage measurements. The results of some of this work were published in 1926 (2 and 3) and again in 1927 (4) and 1928 (5), with further follow-up in 1933 (6).

The possibility of an index constant to biologic reaction derived from a comparative study of the half value layer in phantom was suggested in a publication by Meyer and Glasser in 1926 (3).

I am taking the liberty of appearing before you again in this matter since, in addition to a careful review of our work, we have extended our studies to include increased voltage and filtration and are still seeking the truth with regard to the measurement of r by ionization in its relation to skin and tissue reaction.

Notwithstanding some expressed adverse opinion, we still believe that we are correct in the assumption that the number of roentgens as measured by ionization will vary considerably with respect to a given skin or mass biologic reaction, this depending to a great extent upon variations in ray quality, resulting from changes in voltage and filtration.

From the physical aspect of the problem, the advertisements of manufacturers—that their particular ionometers are independent of the wave length—but add to the confusion, since every physicist well knows that no thimble wall type of ionization chamber to-day can be considered as independent of ray quality.

F. C. Wood, in a recent article (7), requotes the fruit fly experiments of Packard (8, 9, 10) wherein the radiation effect would appear similar, despite variations of ray quality. Aside from any criticism of the method pursued or conclusion drawn, the question still remains whether any inference of parallelism is justifiable between the lethal dose on a *thin layer* of radiosensitive *Drosophila eggs* and reaction of a similar dose to the highly vascular human *tissue mass*.

Packard in one of his conclusions clearly states that: "*The eggs of the fruit fly, Drosophila, can be used as a dosimeter for estimating x-ray dosage.*" There is the further suggestion that the lethal dose of

[1] Presented in synopsis form on Dec. 5, 1934, in a Symposium on Physics of Radiation at the Annual Meeting of the Radiological Society of North America, at Memphis, Tenn.

Drosophila eggs may be a supplement to, or substitute for, iontoquantimetric dose estimation in r, but *"biologic variation cannot now be excluded."*

At the recent (June, 1934) meeting of the American Medical Association, in Cleveland, Hodges (11) reported the results of experiments on animal and human skin, wherein the attempt was made to show that the radiation effect is uninfluenced by ray quality. Some of the material presented reveals such wide variations in reactions that the inference appears inconclusive and would rather tend to substantiate our observations.

Who of you does not apply a greater dosage as measured by ionization with the higher voltage and filtration in deep therapy, as compared with the longer wave length treatment of superficial skin lesions?

If a fixed number of r results in a similar reaction, irrespective of voltage and filtration, then why this disparity in practical application at most of the largest clinics in the country?

Invariably the dosage (expressed in r ionization measurements) is numerically far greater when higher voltage and stronger filtration is employed than with the softer ray, skin therapy technic. A review of the literature and the most recent presentations further substantiates this fact.

Again, at the 1934 Cleveland meeting, and since published (12), MacKee and Cipollaro presented a survey of quality dose measurements as applied in radiation (skin) therapy and came to the conclusion that the erythema (skin unit dose) averages about 325 r (measured in air).

In a report published by Andrews and Braestrup in 1933 (13), a similar survey revealed 400 r as the skin unit dose. In the race to present such material Eller and Mutscheller (14) preceded Andrews by a month with 340 r as the skin unit dose. Some of these authors kindly referred to our "pioneeer" work in this field. In all, the voltage is comparatively low: 75 to 100 K.V., with little or no filtration other than the tube wall.

Turning to higher voltage and stronger filtration—from a Memorial Hospital report (15) one observes that 540 r is the threshold erythema dose of the workers in that institution when employing 200 K.V. and 0.5 mm. Cu filter.

TABLE I.—SHOWING THE RELATION OF IONIZATION MEASUREMENTS TO SKIN REACTION WITH VARIOUS RAY QUALITIES

(As employed in several New York institutions)

Reference No.	Sponsors	Voltage K.V. Peak	Filtration in mm.	r by ionization in air
14	Eller, J. J., and Mutscheller, A.	78 to 97		340 average
13	Andrews, G. C., and Braestrup, C. B.	100 135	0 3 Al	−400 +400 to −500
12	MacKee, G. M., and Cipollaro, A.	100		325 average
15	Memorial Hosp. Group	200	0.5 Cu	540+
Personal communication	Lenz, M., Presbyterian Hosp., Montefiore Hosp.	200 M.R.[1] or 180 C.P.[2]	0.5 Cu 2 Cu	+600 +700−
Personal communication	Harris, William, Mt. Sinai Hosp.	200 M.R.[1] or 180 C.P.[2]	0.5 Cu 2 Cu	−600 +650
Refs. 2–6, inclusive	Meyer, W. H. Meyer and Glasser Meyer and Braestrup Meyer and Mutscheller	75 to 100 130 200 200 or 180 C.P.[2]	0 1/4 Cu 1/2 Cu 2 Cu	+350 +450− −600+ +700

[1] M.R. = Mechanical Rectification.
[2] C.P. = Constant Potential.

From further sources including the Mt. Sinai, Montefiore, and Presbyterian Hospitals in New York City, the information is gained that with 200 K.V. and 0.5 mm. Cu filter, the dose administered approximates 600 r, whereas with 2 mm. Cu filter 700 r more nearly approaches a threshold erythema dose (all measurements in air).

Whereas our earliest work (2) was based on a rather definite erythema reaction with measurements inclusive of back-scattering, our skin unit dose to-day is nearer a threshold erythema with scalp epilation as the actual unit of measure. The calibration of instruments used in our early work also had a greater number of the old R per division of the scale than the standard small r calibration of to-day: therefore, the present measurements, as made by ionization in air, show a curve on a given chart somewhat lower than that first published. Nevertheless, the character and general pitch of the curve remains practically the same.

In Table I a condensed summary of the collected data, inclusive of our own, is presented.

The chart herewith published forms a composite survey of our cumulated experience and is the basis of all our radiation dosimetry. Though some of the comparative data are probably not sufficiently accurate to escape the critical physicist, nevertheless, for the therapist this chart should be of practical value in linking the physical measurements and calibration of

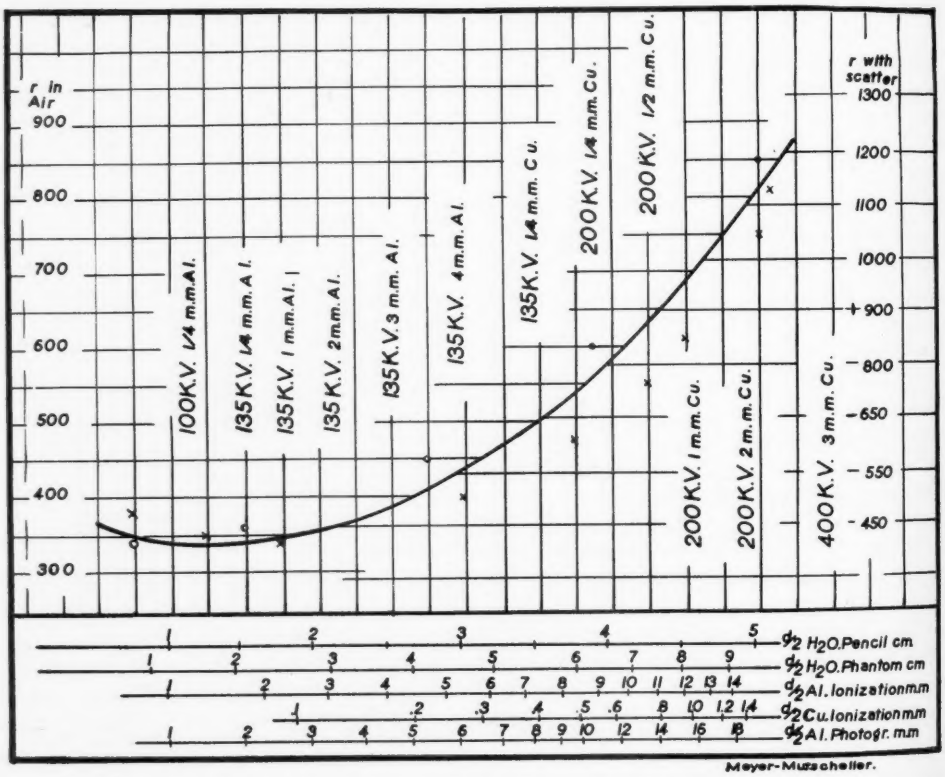

Chart showing the influence of ray qualities on the dose (expressed in r) for a given epilation (erythema) reaction.

(Acknowledgment is made of the writer's indebtedness to Dr. A. Mutscheller for his assistance in checking the physical data as well as in preparing the chart.)

Note: ○ = Data submitted by Glasser; × = Data (experimental) by Meyer.

equipment to the variations of everyday radiation therapy. In the left-hand vertical column the ionization r measurements in air are indicated. To the extreme right appear the approximate r as measured on a large phantom through a large portal (*i.e.*, with back-scatter). Horizontally at the bottom in the first line, the figures represent the half value layers of a pencil beam in water. Below this, for the purpose of ready reference, some other practical qualitative measurements are listed in the approximate position of their respective values.

Since there is to date naught else that visualizes more clearly the relation of quality to quantity, and at the same time permits of simple designation, we adhere to *the half value layer*, in a given substance, as the *measure of quality*.

Various points on the curve (in the above-mentioned chart) indicate, in the vertical column, the quantity in r required for a given skin reaction (epilation, erythema), with the different ray qualities listed at the bottom of the chart. Some of the practical every-day working technics are indicated across the top of the chart, again approximately in their relative position to the actual qualities obtained.

It is, of course, apparent that the higher the voltage and the stronger the filtration the greater is the relative r measurement for a given reaction. In the main, the data on the chart correspond closely to those we reported in our early findings. It will be seen that with low voltage (±100) K.V. and weak filtration (0.5 mm. Al), the epilation (erythema) dose is recorded as about 350 r (in air). At 200 K.V. and 0.5 mm. Cu, 550 to 600 r are recorded, and when +2 mm. Cu as filter is employed, the r measurement in air averages between 650 to 700 r. It might also be mentioned that most of these figures, reported by us many years ago, are in close agreement with the practices of some of the larger institutions to-day.

If one will but observe the ever-increasing half value layer with increasing voltage and filtration, then the reason for quantitative variation with the present-day measurements in r should be evident. Truly mass absorption must be the index of reaction in any given form of tissue.

CONCLUDING DISCUSSION

There are, perhaps, one or two points not sufficiently stressed that appear on the chart.

First, I wish to express my appreciation to the discussants and most particularly to the Memorial Hospital representative. Is it, however, not a question whether reaction on *Drosophila* eggs may be one thing and living human tissue reaction, with its rich vascular and lymphatic supply, another?

A point not evident in the chart but brought out by the discussion is that the measurements are influenced by the wall thickness of the ionization chamber. Frankly, I do not believe that the wide variation in r measurement in relation to skin or biologic reaction is entirely to be ascribed to the thickness of the chamber wall.

Another point deserving of thought is the peculiarly constant index figure that appears: namely, if with a given ray quality one multiplies the half value layer of a pencil beam in water with the figure 150, it is remarkable how close is the estimate of the r required (as measured in air) to result in a uniform erythema skin reaction.

In conclusion, I wish to reiterate my belief that, except for variation in radiosensitivity, in mass absorption will the secret to biologic or, rather, human tissue reaction be found.

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DISCUSSION OF SYMPOSIUM ON PHYSICS OF RADIATION

DR. A. N. ARNESON (New York City): A description of the exhibit will, of course, be a brief repetition of the paper that has already been presented. The exhibit consists of a number of diagrams illustrating the distribution of radiation obtained throughout the average female pelvis in the treatment of cervical cancer, for a variety of port arrangements. These diagrams are shown for target-skin distances of 50 and 70 centimeters.

The size of the pelvic diagram used in the preparation of the charts was determined from measurements made upon several patients with cervical cancer. The measurements were made in a plane passing through the heads of the femora, and the upper border of the symphysis pubis, which was chosen to represent approximately that of the cervix. The average anteroposterior and lateral diameters were 23 cm. and 35 cm., respectively. The distribution of radiation shown for each port arrangement considered, is that which would exist within a pelvis of the dimensions specified. Patients of smaller size would receive a greater percentage depth dose, and those of larger size would receive a lesser percentage dose.

If large fields were used on the anterior and posterior pelvic surfaces, they measured 15 cm. longitudinally and 20 cm. transversely. If two small fields were used on these surfaces, they were 15 cm. longitudinally and 10 cm. transversely. Since the total irradiated skin area on both the anterior and posterior surfaces is the same in all of the diagrams, and the size of the pelvis is constant in each instance, the diagrams may be used for comparing the advantages and disadvantages of the different port arrangements considered.

If two beams are directed straight into the pelvis on both the anterior and posterior surfaces, without tilting toward the mid-pelvis, and if the fields are separated in the mid-line by a distance of 2 cm., then the bladder and rectal regions are spared doses in excess of the amount delivered to the cervix. When radium is applied to the primary lesion, which will control the disease within a distance of 3 cm., or perhaps 4 cm., from the cervical canal, a greater dose will be delivered to the cervix than to the bladder or rectum. The addition of lateral beams increases considerably the dose delivered to the parametrial regions, but adds very little to the dose reaching the mid-pelvis.

The doses delivered to the cervix, and to points 2 cm. apart along a line drawn directly lateral to the cervix in the transverse diameter, are shown within a diagram of the pelvis for each of the port arrangements that have been considered. These values illustrate that the tumor-bearing area receives the greatest amount of radiation when lateral fields are employed. The ad-

vantages of using two ports on the anterior and posterior pelvic surfaces have already been discussed. A six-field arrangement, therefore, employing two fields on the anterior, two on the posterior, and one on each lateral surface, delivers the most suitable distribution of radiation for the treatment of cervical cancer.

The distribution of radiation obtained from two anterior fields has been illustrated radiographically. The level of the cervix was marked with an opaque material, and a flat plate of the pelvis made. Before disturbing either the patient or the cassette containing the film, exposures were made through each of the two anterior ports, with the beams oriented and directed in the usual manner for treatment.

It can be seen that the beams include the promontory of the sacrum, as well as the cervix and uterus. Unnecessary abdominal irradiation is avoided, and the external genitalia are not exposed to the direct rays. The upper border of the fields is at the level of the iliac crests, and the lower border located about the middle of the symphysis pubis. If the fields are 15 cm. long, they will usually extend between these two bony landmarks, which can be used for marking out the pelvic ports on the anterior, posterior, and lateral surfaces.

DR. EDITH H. QUIMBY (New York City): I have been very much interested in this group of papers on the physics of radiation. I think your Chairman is to be congratulated on having assembled such a symposium, and particularly on finding two such satisfactory "pinch hitters" to take the place of absentees.

Each paper deserves more thorough and careful discussion than is possible in the few minutes at my disposal. With the exception of Dr. Stone's[1] and Dr. Arneson's papers, every one is to a certain extent concerned with the physical measurement of gamma-ray intensities. This is one of the most important problems for the radiologist at the present time. We are all anxious to express radium and x-ray doses in terms of the same unit. This anxiety has led in some instances to a premature adoption of the roentgen as the unit for gamma rays. Certain experiments carried out under specified conditions have given definite values for the number of roentgens corresponding to 1 milligram-hour of radium at a distance of 1 centimeter. These experiments have been carried out, for the most part, with small closed ionization chambers, and it has not been possible to comply with all the requirements of the definition of the roentgen. This definition states specifically, "—when all the secondary electrons are utilized, and the wall effect of the chamber is avoided—." For 200 KV. x-rays it is possible to meet these specifications with the standard open air chamber. Within a certain range of quality the small "air-wall" chamber has been found, under proper conditions, to give the same values as the standard chamber. As the energy of the rays increases, it becomes more difficult to build an open air chamber which will meet the requirements. The small closed chambers never did meet them; it simply happened that they gave the correct values, within a certain range. As the wave length decreases, the effect of wall material and wall thickness becomes more important. The size of the chamber, and its distance from the source also come into consideration. Experiments made at the Memorial Hospital, and reported by Dr. Failla at the Fourth International Congress of Radiology, show the importance of these factors. Measurements of the radiation from radium, by means of spherical ionization chambers of various sizes placed at different distances from the source, show an increase in the value of the output as the distance is increased, even up to 10 meters. (Due allowance has been made for the inverse square law, but none for the absorption of radiation by the air.) Scattering from the air in the room, as well as from solid material, has been shown to be a factor which must be considered. With regard to the chamber material, it has been

[1] Published in two parts: RADIOLOGY, February, 1935, **24**, 153–159; March, 1935, **24**, 298–302.

shown that as the density and atomic number of the material increase, the ionization also increases. Various workers have shown that, with chambers of organic materials, the ionization increases up to a wall thickness of about 4 mm., and is constant after that. For this reason they have suggested the adoption of such a chamber as standard for gamma-ray measurement.

It is evident that it is impossible to measure gamma rays in roentgens according to the present definition. The physicist may establish an arbitrary set of conditions for distance, chamber specifications, etc., and say this shall represent the roentgen—in effect, he is changing the definition. And when physicists agree upon such changes, they must keep in mind, as Dr. Meyer has reminded us, the biological applications of the measurements. If, for instance, we decide on an ionization chamber with a wall of 4 mm. of celluloid, we must remember that the radiation within this is not the same as the radiation at the surface of the biological material—*that* is not surrounded by a celluloid wall. The physicist, with such a chamber, can measure the radiation under his set of conditions, and can tell when this is duplicated, but he cannot make biologically accurate measurements when he changes from one set of experimental conditions to another.

In this connection we may consider Dr. Meyer's work on the varying amounts of radiation necessary to produce erythema for different qualities of radiation. From the clinical point of view, this is an exceedingly important problem. Almost everyone is agreed that with increase in wave length, the amount of radiation required to produce this reaction decreases, down to a certain point. Here again comes the problem of how the radiation is to be measured. The question of the use of *Drosophila* eggs as a standard, because of their wave length independence, has been brought up. Actually they have never been shown to be independent of wave length in their response to radiation. It has been shown that, over a certain range, they respond in the same manner as the "air-wall" ionization chamber; that is all. At the Memorial Hospital, where we have compared the effects of 200 K.V. x-rays, 700 K.V. x-rays, and gamma rays, on the basis of ionization as related to three chemical and three biological reactions, as well as to human skin erythema, we have found almost as many different relations as we had experimental subjects. The problem is a very complicated one.

In order to emphasize this, I might mention the values obtained for the number of roentgens emitted per minute per gram of radium, with a filter of 0.5 mm. platinum, at a distance of 1 cm., by a study of various reactions, all being investigated under as nearly identical conditions as possible. With a certain small applicator holding the radium 1 cm. from the skin, by producing the same type of erythema as that resulting from a known quantity of 200 K.V. x-rays, Dr. Arneson and I determined for the radium an output of 88 roentgens per minute per gram. Using the same applicator, with both wheat seedlings and *Drosophila* eggs, Dr. Henshaw found an output of 66 roentgens. With an ionization chamber of exactly the same size and shape as the applicator, Dr. Failla and Mr. Marinelli found an output of 55 roentgens. This demonstrates the difficulty of linking physical and biological measurements. It is impossible to take any one biological reaction, be it erythema, epilation, killing of *Drosophila* eggs, or anything else, and assume that it will express all biological reactions for all types of radiation. It is very fortunate, from a therapeutic point of view, that this is true; if there were no difference in response between different types of tissue, radiation therapy would not offer much clinical hope, Such therapy is built upon an assumption of differential response from various tissues.

The measurement of ionization in liquids, described by Dr. Taylor,[2] seems one of the most promising lines of investigation of the amount of radiation actually delivered within the tissues. Dr. Failla and I made

[2] Dr. Lauriston S. Taylor, of the Bureau of Standards, Washington, D. C., was the leader of this Symposium. He expects to publish his paper later in the year.

some investigations along these lines some years ago, but encountered such experimental difficulties that we postponed further work. I am delighted to know that Dr. Taylor has found a practical method for making such measurements in liquids having molecular structures sufficiently like tissue.

Calculations of the sort presented by Dr. Laurence are of great importance in the development of interstitial irradiation. He has found it necessary to make separate tabulations and computations for every different arrangement of needles. He will, however, probably find it possible to make some simplifications so as to render his data more readily available for the practising radiologist. At the Memorial Hospital we have made similar calculations for the distribution of radiation around needles, and have been able to construct a table (*Am. Jour. Roentgenol. and Rad. Ther.*, 1935, **33,** 315) for dosage when needles are used throughout a lesion. With the type of irradiation in which he is especially interested, in which the source of radiation is outside the lesion, a different type of table would be necessary.

Dr. Stone's report[3] is of great interest to all of us who are concerned with high voltage x-rays. His equipment has some marked advantages over many of the other types, and we all want to know what it does and how it does it.

Dr. Arneson's paper has a more direct clinical appeal than the others on this program. His charts are presented in the Scientific Exhibit, and a question has been asked several times as to their degree of accuracy. Anyone who has made isodose charts knows that values along the axis of the beam should be good, while those along its edges are uncertain. For the purpose for which these charts were intended, namely, a comparison of methods, the charts are of sufficient accuracy to warrant the conclusions drawn. As an actual statement of dosage, they cannot be considered to be closer than about 10 per cent, and possibly some deviations are greater. Variations of this amount are not significant for clinical purposes. It must be remembered that doses taken from these charts are correct only for a pelvis the size of the one used. For a large, fat woman, the dose delivered at a given point might be considerably less.

[3] See Footnote 1, page 203.

G. C. LAURENCE, Ph.D. (Ottawa, Canada): I should like to say something about that number—the ratio between the dose in roentgens and in what we have called milligram-hours per centimeter squared (Imc.-hr.). Some values obtained by different writers have been quoted—they differ somewhat. These differences are due partly to experimental errors no doubt, but mostly to differences in the definition of the Imc.-hr. which they have adopted. We have verified this experimentally by actually making measurements under the experimental conditions called for in the definitions. I have already stressed this unsatisfactory feature of the unit.

Since we have deduced the dose in roentgen from that determined in Imc.-hr. by multiplying by this number, one might perhaps expect that our values in roentgens were dependent on the peculiarities of the definition of the Imc.-hr. adopted. This is not entirely true. The peculiarities of the definition are taken into account in the value of the number. Consequently, the peculiarities are eliminated. In other words, the experimental conditions which obtained during the measurement of the physical variables which are involved in obtaining the dose in Imc.-hr. are either reproduced in determining the ratio between the two units or else correction is made for them mathematically. When this has been done the uncertainty in the dosage in roentgens on this cause is appreciable but not serious, in comparison with biological uncertainties.

Another point raised by Dr. Quimby: she referred to the work they have been doing in measurements of the dosage distributions in tissue in which they have a grid-work of radon units. In these calculations which we have made, we had in

mind more the type of technic in which the radium is placed outside the tumor, placed above it—a technic which, I believe, is more common in Europe and in parts of Canada. In such work the dose does depend greatly on the design of the radium units.

There is another point I would like to make and that is in regard to the relationship between physical dosage and biological effect. The physicist does not claim, does not believe, that biological effects can be expressed in such a way that one can numerically proportionally correlate them with dosage measured in roentgens, independently of the quality.

The variation of the dosage required for epilation with quality which was shown in the slide a few minutes ago, is the kind of variation which the physicist might expect from purely physical considerations. I think there has been misunderstanding on that point.

THE TREATMENT OF ADVANCED MALIGNANT DISEASE[1]

By LIONEL S. AUSTER, A.B., M.D., *New York City*

From the New York City Cancer Institute and Hospital, Dr. Ira I. Kaplan, Director

AS THE education of both the medical and lay public advances, the realization will take hold that the therapy of cancer is a group problem rather than an individual task. This will eventually aid in the reduction of early morbidity and mortality. But at present the material at the New York Cancer Institute and Hospital bears evidence that the common attitude of the profession too frequently is one of fatalism, with an all-too-pervading sense of original omniscience and omnipotence. This impression is based upon the fact that the majority of cases admitted to our hospital are instances of the following serial progression of events: (1) Attempts to treat malignancy in its early stages with an inadequate program of therapy; (2) the recurrence or progressive course of the disease; (3) the baffling prospect of the terrifying morbidity which may precede death, and (4) final release from responsibility by transfer of the patient to a hospital or clinic such as ours, which is unique in its facilities for harboring large numbers of these patients for indefinite periods of time.

This attitude might be condoned if all these patients were indigent persons sent merely for terminal custodial care, but most of them, while late, are individuals whose lives may be, and usually are, extended in comparative comfort for long periods. Many of our patients are discharged home as cured or arrested cases, to return for ambulatory observation, treatment, or subsequent hospitalization, over many years, and our resident population numbers some who have been with us for over seven years.

It is on this account that we have adopted the feeling that, except in obviously terminal disease, we can never give up trying. The purpose of this communication is to attempt to postpone the usual discussion of euthanasia which arises in the presence of late malignancy, and offer some thoughts based upon our not-always-successful experience in the handling of advanced malignant neoplasms, with the hope of mitigating the patient's discomfort and prolonging his life if he can be freed of the active symptoms of disease.

[1] Read before the Annual Conference, Division of Cancer, Department of Hospitals, City of New York, April 10, 1935.

CLASSIFICATION

The treatment of advanced malignancy falls into two general categories: attempts at cure, and palliation.

The initial classification of the patient is determined by whether his lesion is still localized and amenable to extirpation and/or control by a combination of the agencies at our disposal, or whether, in the presence of recurrent, bulky, inaccessible, pathologically resistant or disseminated disease, the most we can offer is palliation and general systemic support, with amelioration of local symptoms.

The facilities at our command are medical, surgical, the use of radiation in the form of radium or roentgen ray, and the newer combination of radium-surgery—any or all of these. The therapy must be applied in all cases with a consideration of the individual patient, and takes the form of general and local measures.

GENERAL CONSIDERATIONS

In the general grouping, the chief difficulties in the late stages of cancer (the term here is used to denote all malignancy) are those of a systemic nature which may be secondary to the disease or its treatment, or may be wholly independent

thereof but accelerated thereby. In the latter group are those degenerative diseases which are most common in persons of advancing years, and, in the presence of the malignancy, the patient's cardiovascular and renal apparatus can nevertheless be the cause of his death, and frequently is. Diabetes and tuberculosis make great headway in the frequently undernourished cancer patient and, except in the presence of terminal states or liver involvement, there has never been a good reason advanced against the feasibility of treating syphilis in these individuals. Indeed, arsenic therapy is usually of considerable benefit from a hematinic and tonic standpoint.

That ill-conditioned state of body and mind comprising weakness, malnutrition, asthenia, anemia, and depression, which we call cachexia, is a symbol of bodily degeneration which, imperceptibly advancing, brings to the late case an unmistakable appearance associated with wasting disease. But frequently our therapy may cause its supervention as well as delay it. In the well deserved acceptance of radiation as the method of choice in treatment of many lesions, the enthusiasm of the therapist must be stayed by the realization of the general systemic effects of this powerful agent. Patients vary in their tolerance of the large doses now in vogue, and the reaction of the hematopoietic system must be carefully gauged, particularly in view of the late effects seen with production of anemias similar to those of the primary type in severity. The use of frequent and adequate transfusions, when blood is available, is imperative in anemias both acute, following hemorrhage, and of chronic course. The liberal administration of venous and hypodermoclyses of glucose and saline solutions during periods of stress, asthenia, and dehydration are urged. Physical therapy, particularly the use of ultra-violet light, cheerful surroundings, adequate nutrition, meticulous care in nursing, and personal hygiene have obvious advantages.

THERAPY OF PAIN

The problem of pain is the most distressing of all—to the patient—in advanced malignancy. Pain almost always occurs eventually in the course of this group of diseases, sometimes very late, and sometimes of evanescent character. But usually when it arrives it is constant, increasing in severity, debilitating, and is probably the most potent factor in the undermining of the morale of these sufferers. The pain may be incidental to the local lesion, may be the result of local extension with invasion of perineural lymphatics or destruction or involvement of sensory nerves, or may be the result of distant invasions which encroach upon tissues far from the primary lesion. These last pains are frequently mistaken for adventitious symptoms in the presumably early course, only to be revealed as the first evidences of definite metastases when the trained observer recognizes their significance. The repeated stories of "rheumatic pains," "growing pains," "arthritis," "intestinal headache," "pleurisy," and "sciatica," in cases of skeletal and pleuropulmonary dissemination, are all too common in thousands of histories.

The treatment of pain must be undertaken with a realization of the causative factors. General medication with hypnotics and analgesics is necessary, and although we feel that terminal stages require liberal use of narcotics, the administration of opiates should be limited in those instances of probable long duration, on account of the dangers of habituation and raising of the threshold of effectiveness. Moreover, it has been found that acetyl-salicylic acid and the coal tar group (sometimes in association with small doses of the barbiturates or even, when necessary, fractional amounts of codein) are usually effective in controlling general symptoms for extended periods. Amidopyrin, acetphenetedin, antipyrin, and acetanilid are analgesic medicaments of increasing potency, in the order named, for the vast majority of pains. Radiation

therapy is of inestimable and dramatic value in controlling the pain of bone metastases. Local nerve or spinal block, or the newer surgical attacks on the parasympathetic system are remarkable measures for the control of regional symptoms.

APPRAISAL OF SURGICAL RISK

At this point it may not be amiss to interpolate a word concerning the general problems confronting the surgeon in these cases. The technical development of the surgeon's art has reached a point beyond which there is little room for improvement except in individual development of skill and the perfection of team work. However, the hazards of these technical procedures are both real and ever-present, though, for the most part, intangible. In fact, the surgery of malignancy at this time has in many cases overreached itself, with the result that many men of wide experience and unquestioned ability have begun to exercise that better judgment developed as a result of these qualities, and are relegating more and more of the pathologically qualified lesions in difficultly accessible locations to the radiation therapist for primary treatment. Moreover, the rôle of radiation in the diminution of initial bulk of radiation-sensitive tumors makes many of them more amenable to later surgical extirpation, just as the local surgical removal of more adult type neoplasms diminishes their accessible bulk to a point at which interstitial or external radiation may prove effective. But the mere fact that a patient harbors a malignant neoplasm immediately makes that individual a greater operative risk. This is especially true of intra-abdominal tumors. We have all seen exploratory operations performed with speed and a minimum of shock, with no actual surgery having been performed in the abdomen, and the patient returned to bed in excellent condition, only to die within the week. It is, therefore, incumbent upon the surgeon to refrain from excessively extensive procedures in patients with recurrent or long-standing, progressive, necrotic, or infected lesions, but to realize that palliative procedures may be of great benefit and give abiding comfort.

CHOICE OF ANESTHESIA

In view of the greater risks in these patients, the choice of anesthesia becomes of even greater importance. It has been found that the development of skill in the use of local infiltration and nerve block analgesia is an essential in the successful treatment of these people. Operations of considerable severity or extent can be performed with lessened danger by this method. For rapid procedures, particularly about the head and neck, in the absence of respiratory embarrassment, evipal-soluble given intravenously has been most satisfactory, giving control over an unconscious patient for periods as long as a half-hour. Our experiences with this agent have been reported recently by Dr. Livingston.

I am personally partial to the use of rectal or colonic anesthesia, preferably with paraldehyde as the base, and possibly the addition of a small amount of ether and oil in instances in which operations of greater length or severity are contemplated. The chief advantage of this method is the apparently semi-conscious state maintained, with absolute analgesia and complete loss of memory of any occurrences. The patient's mental trauma is minimal; he falls asleep in bed and wakes up there. It is particularly adapted for head, neck, and breast work or extensive plastic reconstructions.

Low abdominopelvic operations, urologic and gynecologic surgery, and amputations or other work on the lower extremities are best handled by spinal or sacral epidural injection. This is also an excellent and much to be preferred method for general abdominal work, but the selection of cases must be made with due attention to the general condition of the patient and the presence of active or latent sepsis. In the presence of a distant active infective focus, such as a sinusitis, the intro-

duction of a needle into the spinal canal for analgesia may produce a meningitis.

There are numerous symptoms and situations which arise in advanced cancer patients which are referable to specific neoplasms of regional distribution.

HEAD AND NECK

Brain tumors usually require only custodial care in their late course, the patient needing nursing care and feeding, most of his existence being in partial or complete coma. However, patients may go on for long periods, sometimes living in this state for over a year.

Skin cancer, particularly that of the face, scalp, and nose, still is a fatal disease which runs a prolonged course and presents complex problems in its management. The recurrent basal-cell epitheliomas especially, which, instead of metastasizing to lymph nodes, recur and extend locally, with destruction of soft tissues and of bone, producing severe hemorrhage, infection, pain, and interference with nutrition, must be attacked repeatedly from many angles as the disease progresses. Ligations of major vessels at points of origin and carotid ligations, when necessary, must be undertaken while tissues are still available for a clean approach. Cautery and electrothermic resections are salutary methods for the removal of sloughing bleeding masses. Drainage and local surgical measures should not be withheld from those cases of disease in the cavities of the skull, which often show marked symptomatic improvement and arrest after the release of exudates and necrotic tumor detritus, possibly preceded by nutrient arterial ligation, and followed by successive courses of radiation.

The lesions of the tongue, lip, cheek, gums, salivary glands, and tonsils are pernicious on account of their progressive recurrent nature, partial inaccessibility, and pain. With the exception of the tonsil and its bulky extensions, most of the other mouth lesions are accessible in some degree for local attack in all their stages. The use of endothermic and scalpel excisions is rapidly superseded, however, by the necessity of reliance upon interstitial and topical radiation. Bone necrosis requires incision and drainage of abscesses and eventual sequestrectomies. Mandibular spasms and contractures as a result of radiation effect on tumor, joint ankylosis, or pain must be treated by trigeminal nerve block, anesthesia, and forcible stretching, or masseter or mandibular ramus section. Mouth hygiene, with due attention to teeth and extraction for feeding, is usually overlooked. Deep infections of the submental region and neck require drainage. The eventual inanition as a result of inability to eat or swallow can be forestalled or aided by a simple gastrostomy. We prefer the Janeway type, done under local infiltration analgesia. Irrigations with mild solutions of chlorine-containing fluids are the most effective for control of the intra-oral fetor and indolent ulcerative suppuration, and mouth-soluble tablets of local anesthetic action, such as euphagin or anesthesin, are greatly appreciated for the control of local mouth and pharyngeal pain. Trichlorethylene has given satisfactory results in pain of trigeminal distribution.

Cases presenting defects in the facial walls following extirpation of the neoplasm can often be rehabilitated by proper reconstructive or plastic surgical procedures. Initial therapy in these cases should always be planned with an eye to later reconstruction. The wholesale sacrifice of tissues makes these subsequent repairs increasingly difficult, if not impossible, whereas cases of curable cancer can and should be handled with the end-result in view.

Laryngeal carcinoma is usually seen late but nevertheless has a long life expectancy with great discomfort. Repeated treatment by divided doses of radiation has kept these individuals going if early, low tracheotomy is performed to relieve respiratory embarrassment, and gastrostomy performed for feeding, when indicated. The necessity for *low*, mid-line tracheotomy must be stressed on account

of the fact that the high operation invariably adds to the complexities of the individual's existence because of early infiltration by the advancing, infected tumor. The larynx becomes fixed, the tracheal fistula distorted and obstructed, the tube irreplaceable, and the terminal aspiration pneumonia, with which most of these patients die, occurs earlier. Tracheotomy, moreover, can best be performed with ease and convenience before radiation in advanced cases. When deferred, it must frequently be undertaken as an emergency measure, and the danger of massive necrosis of the devitalized radiated tissues is not unreal.

CHEST

Pulmonary and mediastinal infiltrations will require thoracenteses at increasingly shorter intervals and cardiac support for the vascular obstructions at the base of the heart. Radiation in carcinoma or its equivalent is occasionally of temporary value, usually increasing the patient's symptoms on account of early engorgement and swelling, with possibly a later interval of decrease in symptoms. These patients, however, return soon after their temporary relief and die with massive infiltrations causing complete great vessel obstruction. In this location, however, the lesions of lymphosarcoma and malignant lymphogranuloma may be treated with more success, their diminution of compression symptomatology and radiographically visible bulk often occurring many weeks after treatment is completed.

The treatment of granuloma malignum merits a word in connection with the frequent misconception of the goal aimed at here. The pathology of Hodgkin's disease is one showing a serial progression of lymphoid tissue changes ranging from characteristic cellular hyperplasia to hyalinizing fibrosis. It is irrational to attempt always to treat for complete disappearance because the patient invariably presents masses which include both early and late types of lesions. The early ones of marked cellularity regress rapidly under prolonged radiation. Those in later stages are stimulated to progress in their natural course—that of fibrosis and hyalinization—which represents a healing stage. This is the end-point and should be our desideratum. With radiation applied to effect fibrosis, excessive radiation beyond this point endangers the general body economy and does nothing further for the deep lesions. They must then be watched carefully only for signs of further or recurrent activity and further radiation instituted at properly spaced intervals.

The pneumonias and purulent effusions which occur as terminal states in so many of these patients suggest the paradoxical statement that patients with cancer seldom die of cancer. Their neoplasia is merely the activating factor in a train of circumstances which produces eventual death. Patients with lesions in the head, mouth, pharynx, and larynx usually end with aspiration pneumonia. Post-operative cases of all sorts are prone to cardiovascular collapse and pulmonary infection. Hemorrhage and sepsis are high in the list, and the necropsy findings indicate that a much higher percentage of these individuals die of the ordinary degenerative diseases than we realize or admit, with inanition a provocative factor.

GASTRO-INTESTINAL TRACT

Early gastrostomy in obstructing esophageal lesions, before the patient's malnutrition has impaired his powers of withstanding operative intervention, will cause both local and general benefits to become apparent. The same principle holds true in cases requiring gastro-enterostomy for pyloric obstruction and colostomy for lesions in the lower bowel. Dr. Yeomans' recent analysis has shown the benefits of these procedures by unmistakable statistical and case demonstrations. These procedures are justifiable even in the presence of liver involvement without clinical derangement of liver function. We have seen numerous instances of almost unbelievably extensive hepatic invasion without jaundice until just before

death, because the deposits were fortunately parenchymal without duct impingement to cause biliary obstruction.

Abdominal ascites requires frequent paracenteses, and definite obstruction should merit early operation for relief, since we have seen many instances exemplifying the operability of conditions which terminated in death. There are occasional instances too in which intra-abdominal pathology unrelated to malignancy is encountered, although the medical attendant usually overlooks the appendicitis or strangulated hernia in the face of intra-abdominal cancer.

BREAST

Cancer of the breast presents abundant opportunity for palliative treatment. The removal of bulky masses with either frank or impending ulceration is a mercy, relieving the patient of a foul malodorous lesion which may be either immediately closed or left to granulate for eventual secondary healing or possibly skin grafting. Even the incomplete removal of bulk facilitates the approach by radiation therapy and the control of many otherwise hopeless lesions. These primarily bulky masses are usually of better prognosis than the small infiltrating lesions with rapid recurrence and wide dissemination. In some types of recurrent localized duct-cell tumors, repeated excision with continued repeated radium and x-ray applications have kept patients on the active clinic roster for six and seven years. The very extensive skeletal infiltrations seen in some patients, in which their bones are riddled with metastases, are of relatively better prognostic significance than the single large painful deposit occurring in the spine or head of an extremity. These patients with honeycombed skeletons are usually relatively free of severe discomfort and can be kept going, much as are cases of multiple myeloma, for many years by repeated rotating cycles of high voltage radiation, with, of course, due regard for the blood picture.

The widespread skin infiltrations seen in recurrences described as *en cuirasse* are resistant and relentless, usually killing by their pleuro-pulmonary extension through the lymphatics of the chest wall despite the restraining influence of radiation.

We do not believe in the effectiveness of attempted *radical* surgical extirpation of so-called acute inflammatory carcinoma in young women, primary inoperable carcinoma with bulky axillary involvement or supraclavicular extension, or apparently primary operable lesions, which fall into the inoperable class as a result of skeletal or pulmonary metastases which are picked up by our routine radiological examination of all breast patients.

The sterilization of younger women with mammary cancer by radiation of the ovaries is a theoretically effective adjuvant to local therapy, particularly as regards growth restraint, or at least the elimination of the endocrine stimulation to growth or recurrence in these specialized and differentiated tumors. Although we have as yet insufficient experience in our own series with which to assay its value, the reports from the Radiumhemmet are sufficiently encouraging to warrant its trial.

BONE TUMORS AND NEUROGENIC SARCOMA

Although the giant-cell tumor of cystic character is usually amenable to radiation properly applied, some of these change their nature and become truly malignant osteogenic sarcomas both in appearance and course. The virulence of malignant bone, nerve, and fascial tumors needs no discussion. Their therapy by radiation is usually unsatisfactory except in the embryonal types, and their cure by surgery usually impossible on account of early extension. Nerve block, alcohol spinal block, amputation or the removal of operable necrotic bulk and accessible recurrences are all measures which are justifiable and necessary when possible. Despite the recurrent nature and known malignancy of these mesodermal neo-

plasms, palliative results of surprising effectiveness have been obtained. Fungation, infection, and necrosis must be treated with usual surgical technics. Surgical diathermy and endothermy are invaluable in these instances, particularly on account of their control of hemorrhage.

GYNECOLOGIC AFFECTIONS

A realization of the cause of death in malignancy of the pelvic organs, with the uterine cervix taking first place in frequency of initial lesions, directs the therapy along well-ordered lines. Cervix cancer patients die of hemorrhage and anemia, of sepsis and of uremia. The anemia and hemorrhage occur from eroded craters or from spongy, friable, infected, bulky, fungating masses which grow into the vagina. The control of these symptoms has been almost universally effectual by the application of the methods suggested by Dr. Ira Kaplan. Endothermic resection of the protruding mass of infected tumor-granulation tissue immediately removes the source of the bleeding. Diathermic coagulation of the base restrains further bleeding until the topically applied cork and colpostat containing a relatively small amount of radium maintained for a long period of time can exert its effect, aided by packing. Frequent vaginal, bladder, and rectal hygiene instituted at periodic intervals with changes of the packing is important. This also removes a large infective focus. Following this initial radiation, the external lesion is controlled, and a previously obliterated cervical canal frequently becomes apparent. Drainage of a pyometra can then be instituted, if necessary, by the use of a tube and frequent intra-uterine douches, eventually making the insertion of a radium tandem feasible. High voltage cycles through four pelvic portals complete the program and control lateral extensions and pain in many cases.

In instances in which the pelvis is not completely frozen and the patient is in fair general condition, intractable pain can be effectively relieved by intra-abdominal section of the pre-sacral nerve. Low spinal alcohol block may sometimes be advisable. The urinary disturbances incidental to gynecologic malignancy are those arising first from ureteral obstruction caused not by radiation fibrosis but by peri-ureteral lymphatic invasion with infiltrating tumor tissue. This produces hydronephroses, becoming pyonephroses and pyelonephritides, as a result of ascending infection and a frequent cause of death by sepsis or uremia. Renal operation has not been well borne. Drainage is established by ureteral catheterization and dilatation.

The vesico-vaginal fistulas developed as a result of injudicious use of massive radium dosage administered for short periods, far outnumber those resulting from frank neoplastic invasion with necrosis. (In fact, our impression is that rectal invasion is more frequent.) Their therapy is a bugbear and requires faithful nursing with astringent douches, retention catheters, kaolin insufflations, and the use of urinary antiseptics and sedatives. Mechanical devices, sponges, and operative intervention have been failures in our hands.

Late abdominal extensions with ascites, peritoneal implantations, intestinal obstruction, and distention are the rule in ovarian and corpus carcinoma. Radiation following paracentesis and/or operation with removal of major masses has been sometimes followed by satisfactory regression and clinical cure, although the disease may be present but not prostrating.

KIDNEY AND BLADDER

Renal and adrenal neoplasms in their later stages are almost all relegated to the custodial group on account of their widespread extension, although radiation does effectively control symptoms referable to bone involvement. Bladder and prostatic cancer patients obtain prolonged comfort by the institution of adequate suprapubic drainage, and go on for

long periods until they die of hemorrhage, renal sepsis, or pneumonia.

SUMMARY

No attempt has been made to cover all the possible situations arising in the largest field of medical endeavor—neoplastic disease—but the outstanding features of possible therapy in most frequently encountered advanced conditions have been considered.

The problem of the handling of advanced malignancy has been reviewed also from the general standpoint, with a presentation of the medical, surgical, and radiological measures designed to provide comfort and palliation.

Data in the histories obtained in the types of advanced cases continually referred to the New York Cancer Institute emphasize the necessity for education in the possibilities of treatment in these cases. More particularly do they point to the necessity for trained group handling, with an adequate initial program individually planned for each patient.

1000 Park Avenue

"PIED FORCÉ" OR "DEUTSCHLÄNDER'S DISEASE"

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EVEN though the literature on so-called Deutschländer's disease is quite extensive, new articles on the subject continue to appear from time to time. This fact seems to show that there is still a lively interest in the subject, and the numerous theories which have been developed about the genesis of "pied forcé" show by their lack of unanimity that our knowledge of this condition is far from complete. The fact that many of the views about this lesion are frankly contradictory has given us the urge to summarize what is known about the condition both from a consideration of the literature and from our own experience.

The diagnosis of the affection rests primarily on the radiologic findings, which will be our primary concern. We are taking for granted that the radiologic appearance of Deutschländer's disease is so well known in these days that a repetition of the diagnostic errors into which some have fallen need not be repeated to-day. Due to a mis-diagnosis of sarcoma (Dodd) a patient who had Deutschländer's disease had a Lisfranc amputation performed. In another case (Straus), a metatarsal exarticulation was performed; in such a case, Dr. Markelloff resected a metatarsal and did a bone graft. It is true that the operation was done in this case not through any error in diagnosis but to hasten the process of healing, and at the same time to obtain a histologic section of the diseased bone.

We do not intend to start with the history of the question, a subject sufficiently well covered by other authors, but we will begin our discussion with a consideration of the nomenclature of the disease in question. Among the terms in common use are "fracture de marche," "Marschfraktur," "l'enflure du pied," "Fussgeschwulst," and finally, "Deutschländer's disease." Do these names designate different affections, or do they all name differently the same condition? There is a marked difference of opinion on this point. Most German authors draw a distinction between "Marschfraktur" and "Fussgeschwulst," and identify the latter with "Deutschländer's disease." However, it should be mentioned that in Schinz' book there is no mention of "Deutschländer's disease." Osterland, after reviewing an extensive experience with the subject in question, holds the term "Fussgeschwulst" a poor one, for the lesion in question is primarily one of bone. On the other hand, others, for example, Narvi, speak of "fracture de marche" or of "Deutschländer's disease." Among the Russian authors in general, who base their terminology on the German literature, we find the term "pied de marche" as well as "Deutschländer's disease" to distinguish the latter from "fracture de marche"("fracture de recrue"). We are personally in perfect accord with those authors who are for dropping the term "Deutschländer's disease," first of all because the theories of the embolic and inflammatory origins of the lesion are not confirmed by recent observation, and also because such an affection was described by Breithaupt, in 1855.

But even if we leave out of the question the name "Deutschländer's disease," there still remains the conception of "Marschfraktur" and of "Fussgeschwulst" to be clarified.

From a general review of the symptomatology of the disease in question, it appears that "fracture" occurs generally in military life after a march or a drill, whereas the swelling (*enflure*) occurs primarily in civil life. One comes to the conclusion, especially if one bases one's opinion on the German evidence, that the

first term applies to an acute appearance of symptoms, while the second is a slower process, taking place as the result of a morbid background. But there are, as will be seen later, a whole series of transitional stages between the two forms. That is the reason why we side in with the American and French ideas which unite this whole group under the term "marchfoot" or "pied forcé," without defining the character of the changes in the metatarsals. A common factor on which all authors agree, no matter in what light they regard the process in the bones, is that of overloading the foot. Therefore we think that the term "pied forcé" (forced foot) is that which fits best of all the affection in question.

All cases of "forced foot" may be summed up in two groups: in the first, we shall place the footsoldiers, military men, sportsmen, athletes, and others who can state exactly the moment when their trouble began, and which coincided generally with a forced march, some sporting event, a long walk, or some unaccustomed overloading of the foot. The second group includes those patients whose profession or trade compels them to be on their feet for prolonged periods, such as peddlers, postmen, salesmen, medical men, etc. The patients in this group are unable to state exactly when their trouble started, and it is only in rare cases that they assign the pain in their legs to stumbling, a misstep, or slipping. The difference in the two groups explains the difference in the time at which they consult a physician, just as it explains the difference in the radiographic findings.

Clinically, the affection manifests itself by pain in the foot, which may vary from a slight discomfort in walking to a complete disability, which may require rest in bed. The pain may involve the whole foot or be localized in the involved bone; at the same time there appears swelling and infiltration of the dorsum of the foot, rarely of the sole. At this time it may be possible to palpate a thickening of the bones. Radiographically, there is shown the round or fusiform thickening of the periosteum, usually at the distal end of the metatarsal but rarely in the middle or proximal third of the bone, and a rent across the diaphysis. The question is whether these changes appear in the earliest days of the disease or whether they develop slowly. According to some texts, the radiologic changes in Deutschländer's disease do not appear until the sixth or eighth week of the affection. In "Marschfraktur," on the contrary, they can be detected in three or four weeks. This is the typical picture of the evolution of the disease.

Among the patients we have studied these changes were present in the first radiograph made, but these patients were all civilians, being in the second of our groups. They came to us after they had been on treatment of some sort without success, and often without having had any radiographic studies made. If we check over the histories of these patients, as they have been given by different authors, we shall see that in these cases also the majority of roentgenographic studies were made three or four weeks after the onset of the trouble. Such roentgenographic studies are of no assistance whatever in finding out the early osseous changes. The best opportunity of detecting the earliest changes is afforded military roentgenologists, who are in a position to make a roentgenographic study of their patients at the very onset of the affection. It was Runstrom, of the military hospital of Stockholm, who drew special attention to this point. He made roentgenographic examinations of 45 patients who had "pied de marche" in the first few days (from one to eight) after the onset of trouble. In 26 cases, the changes in the bones could be demonstrated in from one to five days. Similar findings have been reported by other authors. Momburg goes further: he radiographed the feet of all the soldiers who returned from a campaign, even though they had no complaint of foot trouble, and found in a few cases thickening of the periosteum of the second or third metatarsal. We find similar observations in the literature con-

cerning like changes in the normal foot, in cases in which the other foot is "overloaded." This fact is of great importance in the elucidation of the pathogenesis of the affection. The roentgenographic changes may, therefore, appear at any time from a day to several weeks after the onset of the first clinical symptoms, and they may even in some cases precede them. Since the changes seem to be identical in the two groups, the question now is whether the time of their appearance may serve to differentiate the two groups. We do not think that it can. We will now consider the radiographic findings.

Among the various radiographic manifestations of this affection of the metatarsals, we should mention, first of all, the thickening of the periosteum as a result of the structural modification of the cortical layer and the formation of gaps or rents. This spherical or fusiform localized thickening of the periosteum of the diaphysis is not at all characteristic of the affection in question. We see such changes in ordinary fractures of the long bones, especially of thin bones such as the fibula or the metacarpals, and we never entertain any doubt that these changes are traumatic in origin. A metatarsal bone resected by Dodd and Straus in a case of "march-foot" showed typical osseous callus (Fig. 1). The changes in the cortical layer of the metatarsal, which appear as diffuse outlines of the bone at the site of the affection and which seem to extend from the medullary canal to the periphery of the bone, are in no sense anything exclusively found in Deutschländer's disease. This change can be seen in the process of forming callus in ordinary fractures, and it is a manifestation of the participation of osseous tissue in the process of regeneration and development of a new osteoid tissue around the old bone tissue. Unfortunately, most authors take up scarcely at all the question of the split or gap which crosses the metatarsal at the site of this process, and which may even extend into the new callus. We feel that this finding should be discussed in greater detail, for, if we regard the gap as only a fissure or as a "zone de Looser," we get no farther toward understanding the nature of the disease in question.

Fig. 1.

Let us begin with the exterior aspect. The appearance of the fissure in the bone is known by every radiologist, and requires no further comment. The zone of Looser, or the zone of transformation, as the author describes it, and which is seen in rickets, osteomalacia, Paget's disease, and other similar lesions, appears as a straight and clear streak or stripe with sharp edges. Let us remark here that this finding is not a guarantee that we have a zone of Looser and not an ordinary fissure. Schmorl, in a histologic examination of a case of Paget's disease of the tibia which was crossed by numerous clear streaks which Zalinger called typical zones of Looser, found that they were only simple fissures. Now, gaps of this sort in the form of a straight streak are far from being the rule in cases of "forced foot" (pied forcé). We see them sometimes in the later stages of the lesion in which they cross the zone of thickening in the diaphysis. One frequently sees a V-shaped fissure or a zigzag one, a finding that can hardly occur with a zone of Looser. Even more contradictory is the dislocation of the osseous fragments, which is seen in cases of "pied forcé." Therefore, from the radiologic findings we may be dealing with a fissure in some cases, and a "zone" in others.

Let us now consider the anatomic and pathologic findings as they have been reported. Unfortunately, reports on these subjects are rare, and have been made by only three authors, of whom Dodd and Straus speak categorically of fracture, while Markeloff, as the result of his own study, speaks of a zone of Looser. This apparent contradiction in the pathologic anatomy of the process depends on the

differences in the stage of the disease at which the observations were made, and on the static and mechanical condition of the overloaded foot. In acute overload, fissure of bone predominates in the picture. The fine line of fissure was observed several times in the first few days of the disease before the periosteal thickening. There were some cases in which it was the only radiologic sign of the affection. Behr, checking up his own material among 2,146 cases of swelling of the foot, found 877 fractures (41 per cent of the cases). Other authors report an incidence varying from 20 to 90 per cent. Osterland in all of 93 cases regarded the cause of the affection as being the osseous lesion. One must keep in mind the difficulty of determining a fissure radiologically in the absence of dislocation, more or less well marked, of the osseous fragments, and in some cases it is only by examining with a magnifying glass the fine structure of a bone radiograph that it is possible to detect the presence of a fissure. It may well be that it escapes notice in many cases. We should remember that fractures of other bones may not be detected in the roentgenogram if there is no displacement of the fragments. This is the case with fissure which may fall outside the path of the central ray, but which may show up in later roentgenograms when osteoid tissue has formed around the fracture (L. Melnikova, *Zentralbl. f. Chir.*, 1929, **49**). The attempt has been made to establish a differential symptom from the presence of this primary fracture with dislocation so that the two nosologic entities, "Marschfraktur" and "Fussgeschwulst," might be differentiated, but, by what has been said, there is no reason for this distinction. The etiology of the two conditions is the same, and the radiologic picture may show all stages of transitory forms from that of a fine, hardly perceptible fissure to that of a clear-cut displacement of the fragments. According to Runstrom, it is in those cases of primary dislocation in which the fusiform shadow is lacking (19 cases). He explains this by the fact that the blood is poured out into the neighboring tissues, while in fractures without solution of continuity, the blood spreads out under the periosteum and thereby contributes to its rapid thickening and the formation of a shadow in the roentgenogram. This theory seems plausible to us and serves to explain some obscure facts. It then becomes easy to explain all the later manifestations of the affection, by starting with the theory of a primary fissure in the metatarsal, apparent or not, as the beginning of the clinical symptomatology of "pied forcé." The round or fusiform shadow around the diaphysis may be deciphered as a manifestation of the reaction of the periosteum and endosteum in the fracture. The moment when this callus becomes visible in the roentgenogram and the process of its ossification—as clinical traumatology teaches—are different, and depend on local factors, such as the condition of the periosteum at any given moment, the degree of separation of the fragments, the pouring out of blood, lymph, etc. (Runstrom), rather than on individual peculiarities, such as age, constitutional or endocrinal factors. Once formed, the callus follows its usual course of development, that is, it reaches a certain size and then regresses, leaving at the site most affected in the periosteum a faint thickening of the cortical layer in those cases in which there is a complete return to normal.

But another train of events may take place. In the mass of newly formed callus, which is fragile and rich in osteoid tissue, there may form, as is the case in rickets or in some osteodystrophy or other, a transverse split—a zone of transformation of Looser, caused by the same phenomenon of continued overload. It is obvious that if the fissure is formed at the site of greatest pressure in the metatarsus, the callus which develops at the same point in the bone under the continued influence of the mechanical and static factors in the foot will be subjected to the same pressure. This condition will occur in every case in which the patient continues to walk with a callus already formed. As far as we have

been able to judge from what has been published, the patients with a zone of Looser in the roentgenogram were not confined to bed long enough because, according to Müller and Turner and some other authors, the thickening of the periosteum and the margins of the bone in Deutschländer's disease are the expression of the tendency of the body to fortify the threatened section of the bone; but this fortification is often insufficient, and a new fracture takes place across the zone of transformation, sometimes with dislocation of its margins. Those who hold to a osteochondropathic genesis of Deutschländer's disease consider this phenomenon as being a secondary fracture, occurring in the place which is mechanically weakened in the "zone of transformation" of the bone. Now, we have in our possession a roentgenogram which shows a zone of transformation and a fracture, in a case in which the condition came on as a result of a traumatism to the foot. The osseous changes seem to be identical in the different manifestations of "pied forcé," and the time of their appearance is of no importance as a differential symptom.

In the light of the facts established above, let us now consider the genesis of "pied forcé." The theory of the inflammatory origin of the tumefaction of the periosteum falls by itself; the theory of Deutschländer lacks confirmation. The trophoneurotic theory of Turner occupied a place by itself. Without discussing the clinical manifestations of lesion of the peroneal nerve which may produce sweating, sensory disturbances, and so on, let us state that the radiologic findings do not fit in with the hypothesis in question. Trophoneurotic processes, as they occur in other parts of the skeleton, are generally manifested by successive enlargement of bone (for example, the phalanges), which show up in the roentgenogram by coarsening of the trabecular structure, the formation of hyperostoses, infractions, etc. (the tabetic foot, the syringomyelic elbows, etc.), but we are unaware of any trophoneurotic changes which are limited to the diaphysis of a single bone, and which are manifested by periosteal changes without accompanying changes in the osseous trabecular structure. Rarefication of the metatarsus in "pied de marche" (march foot) has been observed by only Turner and his school. We have never seen it. The purely traumatic theory is refuted by the fact that there is no trauma in the majority of the cases, in spite of careful search to find it in the histories.

Special attention should be given to the theories of a statico-dynamic origin of the affection in question. In this regard, Morton has made an interesting calculation. A man of 140 English pounds, with a load of about 90 pounds, loads each one of his feet with one-tenth of an English ton, that is, about 100 kilos. To this should be added the force necessary to lift the foot from the ground during walking and to multiply this by the number of steps per minute—from 60 to 80. But considering the rarity of this affection, one must conclude that load alone is not enough to bring out this affection and that another provocative factor is needed to produce the pathologic changes in the foot. One might suppose it is some endocrine factor (Deutschländer, Müller, Greifenstein), but in this regard it is hardly necessary to more than mention that numerous observations reject this supposition. In 1925, Müller brought out the theory of the osseous insufficiency of the metatarsus according to which the affection might develop by the sole fact of the absence of parallelism between the mechano-dynamic effort and the functional faculty of the metatarsals ("pied forcé," according to our conception). According to Jansen, this supplementary factor is the spasm of the interosseous muscles acting on the hydrostatic pressure of the region of the diaphysis of the metatarsal to increase it. This leads to thickening of the periosteum, with secondary changes in bone structure and to secondary fracture. Ingenious as this theory may be, it can be accepted only by the analogy of muscular spasm of pianists, typists, etc., as by the fact of limitation of lateral passive

movement of the foot which occurs in "pied forcé." The rest of it is only a hypothesis. The stiffness of the toes and the sensitiveness to pressure of the intermetatarsal muscles—symptoms on which Jansen bases his theory—might just as well be considered as secondary to the primary changes in the bones. More convincing are the arguments of those authors who regard functional or structural anomalies of the foot as the cause of the changes. These anomalies may be congenital or acquired. Kirchner, Momburg and others emphasize an abnormal length of the second metatarsal and the jutting out of its head. Others think that the cause is an enfeeblement or fatigue of the muscles of the foot which causes flat foot, with a flattening of the anterior and transverse arches so that the weight of the body is carried directly by the metatarsals, especially by the second, and to a less degree by the third and fourth.

Extensive investigations of the structural and functional insufficiency of the foot have been made by J. Morton. These investigations were concerned primarily with the cause of metatarsalgia, described for the first time by Thomas Morton, and which has a great interest for us. This author has proved that there is no concavity of the plantar arch in the region of the head of the metatarsals. These latter, being loaded in walking or standing, are all in a straight line, and in the same horizontal plane (Fig. 2), but the body weight is divided differently among them according to the structural and physiologic peculiarities of the foot in question. Normally the longitudinal axis falls between the first and second metatarsal, nearer the first, and consequently it is this bone which is subjected to the greatest load. In the triangle of weight-bearing, which is formed by the heel and the heads of the fifth and first metatarsals, it is the latter—or, rather, its sessamoids—which serves as the point of support at the internal anterior angle of the triangle. Weakening of this point leads to alterations in the statics of the foot. Morton established the notion of a weak foot (pied debile) from a structural point of view, which is characterized by the following anatomic peculiarities: (1) The excessive mobility (laxity) of the joint between the two internal cuneiforms and the navicular, resulting in a greater mobility of the first metatarsal. Clinically, this stage of affairs is manifested by exaggerated amplitude of movement of the bone in passive flexion and extension; radiologically, by the enlargement of the space between the first and second cuneiform bones which seems to prolong backward the first intermetatarsal space. (2) The shortening of the first metatarsal (pes atavicus), with a consequently exaggerated pronation of the foot during walking and displacement of the body weight toward the mid-line. (3) A more proximal location of the sessamoids of the head of the first metatarsal so that they are behind a line which passes through the head of the second metatarsal. The result of this is the same as in the case of shortening of the diaphysis of the first metatarsal. (4) The broadening of the second and sometimes the third metatarsal in comparison with the others as a physiologic result of prolonged overload. Dodd verified the findings of "weak foot" of Morton in 14 radiographs of "pied forcé" and found hypermotility of the first metatarsal in 12 cases, shortening of it in two cases, enlargement of the space between the first and second cuneiforms in 12 cases, broadening of the second metatarsal in 13 cases, and broadening of the internal border of the first metatarsal in all of the 14 cases. In the 18 roentgenograms we have found shortening of the first metatarsal in five cases, displacement of the sessamoids in 11 cases, less definite displacement in four cases, thickening of the internal border of the first metatarsal in eight cases, less definite thickening in six cases, definite enlargement of the space between the first and second cuneiforms in 14 cases, questionable enlargement in two cases, thickening of the diaphysis of the second metatarsal in seven cases, and thickening of the diaphysis of the third metatarsal in three cases.

We would like to call attention to a fact hardly mentioned in the work of Jansen which may play a rôle in the genesis of the changes in the metatarsals in "pied forcé," that is, the division of the load at the moment the heel is lifted from the ground when all the weight of the body is carried on the line of the heads of the metatarsals and on the base of the toes. As can be seen in the diagram of Morton (Fig. 2), this line starts on the sessamoids of the first metatarsal and passes to the head of the fifth. In case of shortening of the first metatarsal and backward displacement of the sessamoids, the internal end of this axis is also displaced backward and crosses the diaphysis of the metatarsals before their middle third, that is to say, at just the point of predilection of the formation of fissures and of thickening of the periosteum in cases of "pied forcé." There results an appearance of elongation of the metatarsals, especially of the second and third, and consequently the increase of their overload in walking.

In résumé, we have come to the conclusion that the malady in question is the result of overloading the foot in individuals whose foot is functionally and anatomically weakened. The anatomic changes undoubtedly give rise to the clinical symptoms. In certain cases, because the foot adapts itself or because of extreme overload, these changes may evoke no clinical symptoms whatever; in other cases the subjective symptoms and objective findings may appear perhaps as the result of excessive demands on the function of the foot even though this demand be a very short one, as well as after a prolonged overloading of the foot and in cases in which the necessary rest has been neglected. In this case it is, to use an expression of Dodd, "an autotraumatic complication of a subacute affection." According to the views of Osterland, the fissure in the bone is the result of an internal regrouping of the atoms in the osseous trabecular structure and the formation of "a line or a zone of slipping" which is the forerunner of the formation of a fracture. The phenomena of regrouping which take place in the crystalline structure of the bone are identical to those which are observed in stressed metal as was observed by Henschen by micro-radiologic analysis. The other changes which we have described above consist in the reactionary expansion, or of compensation of the corresponding metatarsals. In place of a round or fusiform shadow, characteristic of "pied forcé," we have a widening, which may extend through the whole diaphysis, only reserving the head and base of the bone. This localization corresponds to the point of insertion of the interosseous muscles as indicated by Jansen. One might conclude that their hyperfunction would result in an excessive irritation and a condensation of the periosteum, as we have observed on a few occasions at the point of insertion of the tendons in bone.

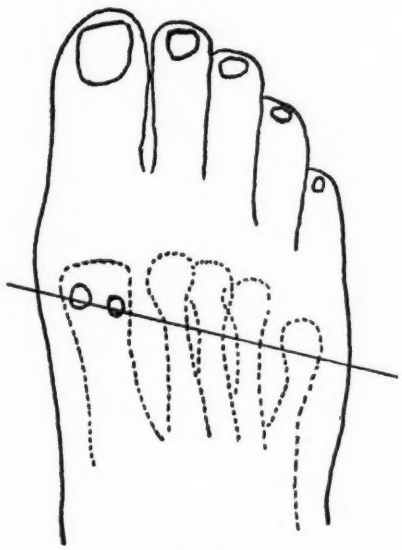

Fig. 2.

A few words about the age of the patients might be in order. The majority of authors speak of the second and third decades, but rarely of the fourth. Turner published a case of "pied de marche" in a man of 60 years. It is generally supposed that early age, with the suppleness and power

of adaptation which the bones and tendons have, is less subject to this affection. Nevertheless, the ages of 16 and 17 figure largely in the reports of most authors (Reckand). We have seen a typical case of acute "forced foot" in a little girl of ten years.

The affection described under the names "pied de marche," "fracture de marche," "Deutschländer's disease," seems to be the least justifiable of all. "Pied surchargé" (overloaded foot) seems to be the term which best fits the malady in question. The analysis of each radiologic symptom, taken by itself, shows that the fissure and the fusiform shadow which surrounds it are the most constant and characteristic symptoms. Moreover, some anatomic alterations may precede the subjective appreciation of the trouble and thereby emphasize the subchronic nature of the process. Of all the theories which have been proposed—inflammatory, traumatic, neurogenic, or functional insufficiency of the foot—it is the latter which deserves greatest attention. Starting with the findings of Morton and Jansen, we come to the conclusion that there are two classes of alterations in the metatarsals as shown radiographically; among the first there are the symptoms of "weak foot," described by Morton, to which there should be added the diffuse thickening of the metatarsal diaphysis. It is possible that hyperfunction of the interosseous muscles plays a rôle in the thickening of the periosteum. The second class of changes is the spherical or fusiform thickening limited to the middle third of the metatarsal. This shadow is of a typical periosteal callus, developing around a primary fissure of bone. The appearance of the fissure is the result of a regrouping of the internal atomic crystalline structure as was shown by Henschen. The cause of the fissure of the bone is the displacement of the weight of the body from the head of the metatarsals toward the mid-line, favored by the anatomic conditions and the structure of "weak foot." Clinically, the affection may have an acute onset; in these cases the radiograph may show osseous changes in the very first days. In other cases, the lesion develops more slowly, so that there is no fissure in the first radiographs; it is the bony callus, which forms more slowly that becomes the first symptom of the affection to be seen radiographically. "Pied forcé" has no relationship to either age or sex.

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THE RELATION BETWEEN AGE AND RADIOSENSITIVITY OF *DROSOPHILA* EGGS

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MANY of the fundamental problems regarding the effects of short radiations on living cells can best be solved by the study of the reactions which these rays produce on small biologic test objects. The effectiveness of different wave lengths, the effect of divided doses, of equal doses delivered at high and low intensities, the changes in the sensitivity of cells during mitosis, and the measurement of x- and gamma-ray doses are questions to which the reactions of comparatively simple organisms can often give clear answers. For testing quantitative effects of radiations, the eggs of the fruit fly *Drosophila* are undoubtedly superior to all other test objects. The flies can easily be obtained and reared, and they lay eggs throughout the year in large quantities. The eggs are so small that radiations produced at ordinary voltages suffer practically no differential absorption; the entire egg is uniformly irradiated. Finally, the proportion of eggs that survive or are killed by a definite dose of any wave length is remarkably constant if the experiments are always performed in precisely the same way. However, if the technic of collection and exposure is altered, the quantitative results differ. The reason for this lies in the fact that the eggs develop rapidly, and during this process their sensitiveness to radiations changes greatly. If the samples that are exposed are not of the same average age, their response to equal doses will be very different. The object of the present experiments is to determine as precisely as possible the changes in the sensitivity of these eggs from the moment they are laid, shortly after insemination, until they are about five hours old, at which time they have already passed the stage when the gut is formed.

The methods of collection and irradiation have already been described in detail (2, 4, and 7). Flies from a pure culture of wild *Drosophila*, inbred for many generations, are transferred to clean milk bottles and given special food consisting of about twenty parts of fermented banana and one part of Fleischmann's yeast. This is rubbed through a sieve and thus thoroughly mixed, and spread thin on pieces of black filter paper (Scleicher and Schüll, No. 551) which have been wetted with banana juice. The bottles are now put in an incubator at 26° C. and left undisturbed for two hours, at the end of which time many eggs will have been laid. These are now transferred to another piece of wet filter paper by means of a small camel's hair brush, and crowded together in a single layer. They are then placed in a moist chamber from which any stray flies are excluded, to prevent the possible addition of a crop of younger eggs. If it is necessary to carry them some distance to the x-ray machine, they should remain in this chamber until the time of exposure. Precisely one hour after the end of the laying period they are irradiated, all of the slips with eggs being exposed simultaneously, one after another being withdrawn when each has received the desired dose. In order to avoid the effect of scattered radiation, the slips are supported on gauze held in a light wooden frame of such dimensions that the wood lies outside of the path of the direct beam. This is a necessary precaution, for the eggs are extremely sensitive to small amounts of soft scattered rays. During exposure, the gauze under the eggs is kept moist with banana juice. Both before and after irradiation, the intensity of the beam is carefully measured by a thimble chamber previously calibrated at the same voltage and filtration with a standard open ionization chamber. The maximum exposure should not be more than 25 minutes, and the intensity, not less

TABLE I

Age of eggs	50% survival dose	Relative sensitivity	"Standard Deviation"
Standard sample	187 r	100.0%	
0 min.	290	64.5	±5.61
30 "	260	71.6	4.52
60 "	247	75.7	7.02
90 "	163	114.7	2.22
95 "	174	107.5	
120 "	183	102.0	3.54
140 "	229	81.5	
150 "	366	50.8	4.15
180 "	861	21.7	1.44
210 "	675	27.7	1.94
270 "	861	21.7	1.62
330 "	1,044	17.9	0.73

TABLE II.—SENSITIVITY OF TWO SUCCESSIVE COLLECTIONS OF EGGS

Dose 213 r in 10 min.

First collection	Dose from curve	Second collection	Dose from curve
47.1%	196 r	56.4%	171 r
44.0	206	58.1	167
35.7	233	67.4	145
46.3	198	64.2	152
41.4	214	61.8	158
35.9	233	56.9	170
39.9	219	61.9	158
40.5	217	55.9	173
Av. 41.4%	214 r	60.3%	162 r

than 5 r/min. Higher intensities, obtained by varying the amperage and distance, are preferable since they permit comparatively brief exposures. These precautions must be taken if precise results are desired.

The exposed samples are now kept at room temperature in a moist chamber. Under these conditions they hatch out in from 36 to 48 hours. However, some flies do not lay their eggs immediately after insemination but retain them for some time. Such eggs are already well advanced in development when they are deposited; they are highly resistant to x-rays, and they hatch out many hours before the others. If the samples are examined on the day following the exposure, these eggs that have already hatched can be counted. Their number is subtracted from the total, which is determined the next day. The living eggs can easily be distinguished, for they are represented by the empty shells left behind by the larvæ when they emerge. These shells are wrinkled bags of parchment-like material, and are wholly different in appearance from the dead eggs, which remain plump. Eggs which are treated in this way constitute what will be called "standard samples." The proportion of such eggs that survive after receiving measured doses serves as a standard with which to compare the behavior of other eggs which, because of their different age and stage of development, differ also in sensitivity.

When standard samples are exposed to a definite dose, measured in roentgens, a definite percentage of the individuals survives and hatches out as larvæ. A record of eight such tests is shown in Table II under the caption "First collection." The average percentage hatching is 41.4, the maximum deviation of a single test being 5.7 per cent, and the minimum, 0.0 per cent. After many such tests have been made with doses ranging from 50 to 400 r, the data are plotted on co-ordinate paper, the proportion of survivors being shown on the ordinates, and the doses, on the abscissas. These points fall along the smooth curve shown in Figure 1. By means of this curve, the doses needed to produce any desired survival rate can readily be determined.

Conversely, the curve can be used to measure dosage. For, if a definite dose results in a fairly definite proportion of survivals, then that proportion indicates the number of roentgens which were delivered. The application of this method is shown in Table II in the column labeled "Dose from curve." Here the number of roentgens corresponding to each percentage of survivals is taken from the curve. The average of all the individual doses is 214 r; measured by the dosimeter, the dose was 213 r. So close a correspondence is not often obtained; on the other hand, a difference greater than 5 per cent is rarely found.

Now, it is obvious that this method is of value only so long as the different standard samples maintain a constant average sensi-

tivity. The term "average" is used because such samples are composed of eggs which differ from each other in age by about two hours, that is, by the length of the collection period. They differ also in sensitivity. But experiments conducted during the past few years have demonstrated that the response of heterogeneous populations of this kind is indeed constant, provided that the method of collection and irradiation is not changed. If the percentages of survivors in a number of samples which have been given the same dose differ widely from each other, the experimental technic has been faulty.

The relative sensitivity of *Drosophila* eggs of different ages has already been studied by Henshaw (3). In his experiments he used samples of eggs obtained during a two-hour collection period, exposing them at various intervals thereafter. It is evident that by this method only the average sensitivity can be found; the susceptibility of eggs of definite ages will not be revealed. The relative sensitivity is determined by comparing the doses needed to kill a certain proportion of the eggs in samples of different ages. He finds, in general, that susceptibility increases somewhat as the eggs develop, the maximum being at the age of two hours. It then falls abruptly during the next hour, and subsequently rises and falls again to a small extent. The actual amount of these changes is uncertain because the results of his three experiments do not agree satisfactorily with each other.

The relative susceptibility of eggs of definite ages and stages of development can be determined precisely by using samples composed of individuals all of which are laid at the same moment. These are very difficult to obtain. However, if the eggs are collected during a thirty-minute period instead of the usual two hours, they will be of nearly the same age. Usually the flies in a mass culture do not lay their eggs at once when they have received their special food, but begin about fifteen minutes later. Thus the eggs, at the end of a thirty-minute period of collection, differ in age from each other by not more than fifteen minutes; practically all of them are in the two-cell stage, few having divided more than once. They constitute a fairly homogeneous sample. The number laid in this short time is not large but is sufficient for experimental purposes. During collection, the cultures are kept at 26° C. in an incubator. Subsequently, the eggs are properly arranged on slips of wet filter paper, and then returned to the incubator, where they remain until the time of exposure. Samples have been irradiated at thirty-minute intervals and at some intermediate points, commencing directly after the end of the laying period. The age of the eggs is reckoned from the end of this period. In all of these experiments, the x-rays were excited at 120 K.V., the tube current being 5 ma.; the filter consisted of 0.25 mm. copper and 1.0 mm. aluminum. The doses were so adjusted as to result in survival percentages ranging from 85 to 30 per cent.

In Figure 1 are shown the results of experiments in which the eggs were irradiated at intervals of one hour, beginning thirty minutes after the end of the collection period. The remaining data obtained from tests made at the other time intervals have been omitted in order to simplify the figure; they appear in another form in Table I and Figure 2. The points determining the course of each curve are, in many instances, the average of several separate tests in which the same doses were given on different days. For comparison, the curve showing the reaction of the standard sample has been added. The latter is based on data obtained from a very large number of experiments carried on during the past six years.

When these curves were fitted to each set of data, it was found that they were all practically alike, differing from each other and from that of the standard sample only in the scale of their abscissas. If, by changing this scale, they are made to coincide at any point, they coincide also at all other points. Thus the sensitivity of the eggs and their stage of development does not

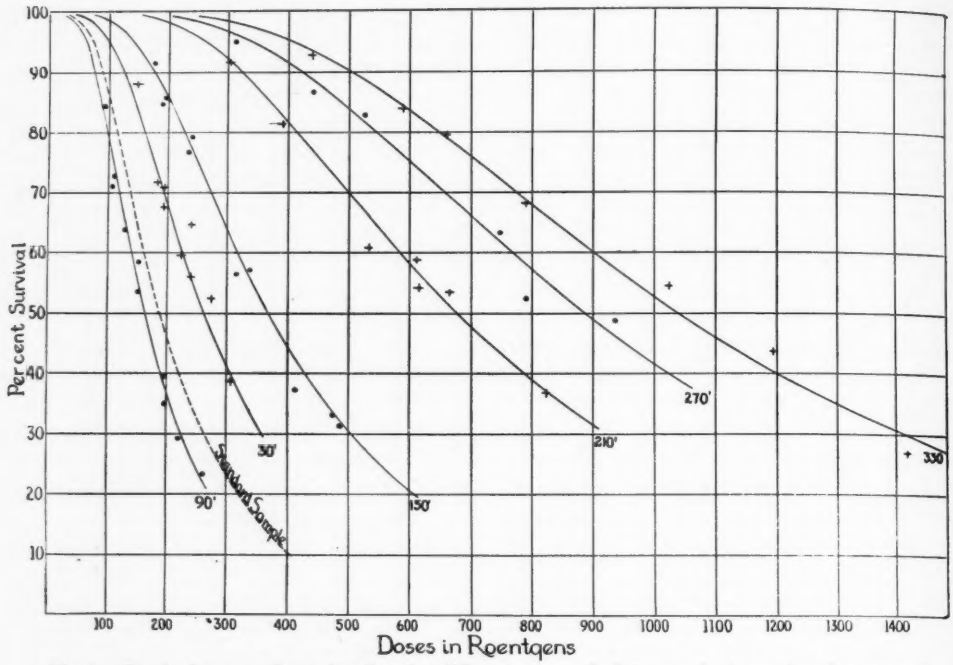

Fig. 1. Survival curves of eggs irradiated at different ages, and of the standard sample, whose average age is approximately 120 minutes.

affect the fundamental nature of the curve. This is true whether the curves express the reaction of samples of eggs composed of individuals all of which are in the same stage of development, or of samples made up of individuals which differ considerably in age and sensitivity. In this respect they are wholly unlike those figured by Henshaw (2), who finds that his survival curves for eggs of different ages pursue irregular courses, and cross each other in some instances.

The wide differences in sensitivity between old and young eggs are at once apparent. The 50 per cent survival dose for eggs that are 90 minutes old is 163 r; for eggs that are 330 minutes old, it is 1044 r. The former are thus more than six times as susceptible as the latter. This dose for eggs of the different ages tested is given in the second column of Table I. It is apparent that the number of roentgens needed to kill half of the eggs grows progressively smaller as the age increases up to 90 minutes; thereafter it increases steadily except for a noticeable decrease in the case of eggs that are 210 minutes old. The figures in the third column of Table I show the relative sensitivity, the sensitivity of the standard sample being 100 per cent. They are obtained by dividing the dose in roentgens needed to kill half of the eggs in the standard sample by that required to kill the same proportion of eggs of each age.

The points which determine the course of the different curves shown in Figure 1 do not always lie close to the curves but are found at various distances above or below them. The departures in the case of the 90-minute eggs are very small; for the 30-minute eggs they are comparatively large. It is important that the amount of divergence from the average be measured in order that the degree of consistency of the results can be determined. The Standard Deviation, shown in the fourth column of Table I, is such a measure. For the 90-minute eggs it is ± 2.22 per cent. This means that approximately two-thirds of all the tests depart from the expected value by less

than this amount. These very consistent results are not found in tests with the 60-minute eggs. The Standard Deviation of differ considerably in sensitiveness. The results of repeated tests, therefore, vary much more widely.

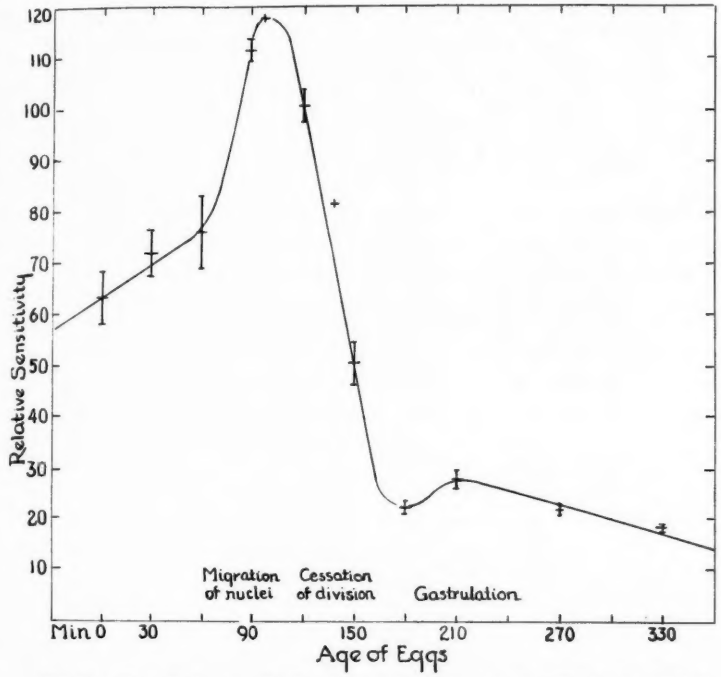

Fig. 2. The relative sensitivity of eggs of different ages. The long vertical lines drawn through the short horizontal lines, which indicate the sensitivity of eggs at each age, show the magnitude of the Standard Deviation for the observations made at these points.

the latter is ±7.02 per cent. In Figure 2, these values are shown graphically by the length of the vertical lines drawn through the points which mark the relative sensitivity of the eggs of each age. When less than ten separate tests were made on eggs of a definite age, their Standard Deviation was not calculated. The degree of consistency in the results of repeated tests on eggs of each age is evidently correlated with the rate of change in the relative susceptibility and with the rate of mitotic activity. When the sensitivity changes slowly, as it does in eggs that are four hours old, the different samples are about equally susceptible, and respond about equally to the same dose. But the reverse is true of 60-minute eggs. The different samples, because of the method of collection, are not of precisely the same age, and, therefore,

The changes in susceptibility during the first three hours of development are correlated with definite embryonic conditions. Shortly after the eggs are laid, nuclear division begins and continues at the rate of about one mitosis every ten minutes, for nine divisions. The nuclei thus formed migrate to the periphery, where they become surrounded by islands of protoplasm. During this period, the sensitivity increases rapidly, reaching a maximum about 100 minutes after insemination. At this time the first evidence of differentiation appears. This consists in the formation, at the posterior end of the egg, of the pole cells, which later give rise to germinal epithelium. The eggs are now also highly susceptible to mechanical manipulation, whereas before this time and afterward, they are not. The next developmental stage con-

sists in the formation of cell walls between the nuclei, which at this time have ceased to divide. With this cessation of mitotic activity, the sensitivity of the eggs falls abruptly to a low point which is reached about 180 minutes after insemination. Subsequently cell division is resumed and invagination occurs. This stage is associated with a small increase in susceptibility. Thereafter, the embryo grows more and more resistant.

Studies on the effect of x-rays on other stages in the life cycle of *Drosophila* show that susceptibility is greatest when physiologic and morphologic changes are in progress. The unripe egg is comparatively resistant (9 and 12), but its sensitiveness increases during the period of maturation, fertilization, and early cleavage, reaching a maximum at the moment when the embryonic cells begin to differentiate. It increases again during gastrulation, and once more when the pupa undergoes reorganization. In the intervals between these periods it decreases steadily. The adult fly is very resistant. Mavor (5) finds that the dose which kills half of the adults in a sample is eighty times as great as that needed to kill half of the embryos. Thus, the statement that embryonic and immature cells are more sensitive than adult cells is true in general, but the most susceptible cells are those that are undergoing a transformation from a less to a more specialized condition.

The average age of eggs composing the standard sample is about 120 minutes, but some individuals may be as young as 60 minutes, and some as old as 180 minutes. There are few of these, however, but it is remarkable that the average sensitivity of such samples should remain constant from year to year. Obviously, the egg-laying rhythm must always be about the same, if the method of collection is not changed. But occasionally this rhythm is altered, with the result that the sensitivity of the sample is lower than expected. This may happen if, at the end of one period of collection, the flies are given fresh food and induced to lay more eggs. Since the process of removing the first food and inserting the second does not greatly disturb them, they often begin to lay actively at once, and then after a varying time, practically cease; this behavior I have frequently observed. The result is that at the time of irradiation the average age of such eggs is greater than that of the eggs in the first sample in which egg production was fairly continuous. The difference in sensitivity between two such samples is illustrated in the experiments recorded in Table II. In these tests, the flies were kept at room temperature on the laboratory table where their behavior could be watched. The records of samples from the different bottles are shown separately. The dose of 213 r, given to both sets of eggs, should result in a survival rate of 41.7 per cent, as shown by the curve. In the first test, the scores of the different samples vary from 35.6 to 47.1 per cent, the average being 41.4 per cent, that is, practically the expected ratio. The record of the second test, made immediately after the first, shows that the average sensitivity is much lower. The survival rate of 60.3 per cent corresponds to a dose of 162 r. This figure, divided by the actual dose, gives the relative sensitivity of the samples. The average is 76 per cent of the expected value. When the same flies were tested on the following day, the first collection of eggs showed the normal degree of susceptibility. Since this change in the rhythm of egg-laying often occurs under these circumstances, it is evident that in carrying out experiments with *Drosophila* eggs, the flies should not be induced to lay a second lot of eggs immediately after they have produced the first.

DISCUSSION

The sigmoid shape of the survival curve shown in Figure 1 indicates that there is a wide variation in susceptibility to x-rays among the eggs used in a single experiment. Some that are highly sensitive die after receiving a dose as small as 50 roentgens; others which are resistant remain alive after an exposure of ten times that amount,

while the sensitivity of the majority, which succumb to doses of intermediate magnitudes, lies between these two extremes. Similar survival curves which illustrate the fact of variation are obtained in experiments on the rate of hemolysis of red blood cells in water, on the number of bacteria or spores killed by phenol, and on the insecticidal action of various chemicals. Even though the biologic material is selected with greatest care to insure uniformity, the individuals always show morphologic and physiologic differences, which are responsible for this variation in sensitiveness to toxic agents.

The survival curve is, therefore, an expression of this variability in the susceptibility among the eggs composing each sample. Since the curves representing the survival rate of eggs of different ages are fundamentally alike, it may be inferred that, in the samples which were used, the proportion of individuals which were more sensitive or less sensitive than the average remains practically the same. The youngest eggs, irradiated when they are in the one- or two-cell stage, show the same degree of variability as do the oldest eggs, exposed when they are already past the gastrula stage.

Henshaw (2) arrives at a very different conclusion. He finds that the survival curves of eggs of various ages differ from each other in a marked degree. Some resemble those shown in Figure 1, while others are irregular, having "a level part somewhere in the middle region." The latter characteristic is due, he believes, to the fact that the samples contain eggs of different ages. In view of the experimental results reported here, this conclusion cannot be correct. More probably, during the period of collection, the egg-laying rhythm of the flies in some of his cultures was altered in the way already described, the effect being that among the several lots of eggs exposed simultaneously in a single experiment, some were far more resistant than others. The result of such a test must necessarily be misleading.

The use of the survival curve as a biologic method for measuring x-ray dosage has already been briefly described. The precision of this method is surprisingly great if due attention is paid to details of technic. However, it is of value only if the course of the curve is constant, that is, if the sensitivity of the standard sample does not change. The experience of several years has proved that in this respect the eggs are very uniform. This is true when different strains of wild *Drosophila* are used for stock. I have tested flies obtained from New York, Florida, Oregon, and from Sweden, and have found no appreciable difference in their reaction to equal doses. In Germany, Jüngling and Langendorff (4) have carried on similar experiments with native *Drosophila*, and report that the survival curve is "practically identical" with that of the standard sample shown in Figure 1, the half killing dose being 190 roentgens. The small differences found at some other points are within the range of experimental error. In all probability, eggs from any stock of these wild flies will be found to be equally sensitive. If, therefore, a stock is accidentally lost, a new one can be substituted even in the midst of a series of experiments.

It should be emphasized that the sensitivity of the standard sample remains constant only when the eggs are collected and irradiated according to the technic here described. If the latter is modified by changing the length of the collection period, or the time elapsing between the end of that period and the moment of exposure, the average sensitivity will also be changed. But it has been shown that the mortality curves based on experiments carried on under these different conditions are precisely like that of the standard sample, except in their scale of abscissas. They can, therefore, be used in the same way as the standard curve in the measurement of dosage. Not all would be equally useful for this purpose. Eggs exposed when less than 90 minutes old are changing so rapidly in sensitivity that the results obtained from them will vary widely: older eggs are more satisfactory. Whatever kind of sample is

used, the technic of collection and irradiation should be exactly the same in every test.

The eggs are equally sensitive to x-ray beams of widely different intensities. This has been clearly shown by Sievert and Forssberg (10 and 11), who tested the reaction to beams ranging in intensity between 2.8 and 4,690 r/min. When delivered at rates lower than 5 r/min., the rays are only slightly injurious, probably because the eggs during the necessarily long exposures have a chance to recover in part. Under such conditions, the survival curve is very different from the normal; the most susceptible eggs are quickly killed, while the resistant individuals remain alive even after large doses. On the other hand, doses delivered at very high intensities kill a larger proportion of eggs than similar doses of moderate intensity; but equal doses, delivered at intensities usually available, produce practically equal quantitative results. The absence of a *time factor* is a point in favor of this biologic material, since no correction for it need be made in the experimental results.

Finally, the course of the curve is constant, regardless of the wave length of the incident beam (6 and 8). Equal doses of x-rays generated at potentials ranging from 12 to 550 K.V. kill equal proportions of these eggs. This is also the conclusion of Glocker and his collaborators (1), who used homogeneous beams of 0.54 and 1.54 Å., and of Henshaw (3), who concludes that the effects produced by 165 and 700 K.V. x-rays are substantially the same. When gamma rays are used, the survival curve showing the relation between dosage in millicurie-hours and the percentage of eggs surviving has precisely the same shape as the x-ray curve. This observation has recently been confirmed (4). Indeed, any other result could not be expected since the curve is an expression of the normal variability in sensitiveness of these eggs to radiations.

The evidence presented here demonstrates that *Drosophila* eggs are especially useful in studying the effectiveness of x-rays. Their sensitivity is the same even though they are obtained from stocks derived from widely separated parts of the world. However, the sensitivity changes in a definite way with their age and stage of development. For this reason the experimental conditions must be most carefully regulated.

SUMMARY

The radiosensitivity of *Drosophila* eggs increases rapidly during the early stages of nuclear division, attaining a maximum when the embryo shows the first sign of differentiation. Thereafter, it falls abruptly, but rises a little during the period of gastrulation. It then declines slowly.

The course of the survival curves for eggs of different sensitivities and stages of development remains constant. It is an expression of the variation in sensitiveness of the individual eggs composing the samples.

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INTRAVENOUS UROGRAPHY IN INJURIES TO THE GENITO-URINARY TRACT

By WILLIAM J. CORCORAN, M.D., *Scranton, Penna.*

THE introduction of opaque substances into the genito-urinary tract has revolutionized the entire field of urology. While the injection of sodum iodide by the retrograde method has been a distinct advance in urologic diagnosis, the intravenous administration of substances excreted by the kidneys has been a greater one as far as injuries are concerned. Recently a substance, Hippuran (sodium-ortho-iodo hippurate) has been introduced which can be administered by mouth. Neither method will probably ever supplant the other in a universal way. In some cases the intravenous and retrograde methods will be employed; in others, the retrograde and the oral administration will be used.

The retrograde method gives no indication as to the function of either kidney except indirectly, through the demonstration of abnormality, whereby disturbance in function is presumed. The intravenous method gives one an idea of the excretory power of each kidney at least in so far as that particular substance is concerned.

The writer has just recently obtained some hippuran and has not used it, except in one case. It was used in a case in which a diagnosis of tuberculosis of the kidney was made and found at operation to be correct. Many diagnoses in the genito-urinary tract will be made, accepted, and the patients operated upon, with only one method of administering the opaque substance being employed. In some cases

Fig. 1. Roentgenogram made 24 hours after the injury.

Fig. 2. Roentgenogram made five minutes after the intravenous injection of 15 c.c. of Neo-iopax.

Fig. 3. Roentgenogram made 15 minutes after Figure 2.

Fig. 4. Roentgenogram made 10 minutes after Figure 3.

this will be sufficient but in many others it will not. The writer has seen a case in which the introduction of neo-skiodan showed a poorly functioning kidney; the retrograde method was employed and a perfectly normal pelvis, calices, and ureter were seen. The intravenous method was again employed with much better results than the first one.

One reason why the retrograde method will not be used in many cases in which it should be, is that so few can do it. Another reason reacting against it is the apprehension on the part of the patient.

Referring physicians in many instances do not know the difference between the different methods, and will be content to accept what information is given them by the roentgenologist after only one method is used.

Different ways of arriving at the same conclusion are always accompanied by considerable controversy. While several methods may be equally good, some individuals claim that some one method is the one *par excellence* and that the others are not so good: witness the different claims of roentgenologists for and against the intravenous and oral methods of cholecystography. One individual may obtain remarkable results with one method and find that his percentage of error is much higher with the other. The reason lies in the fact that he is used to the one and not to the other. There is also the added fact that he may not carry out the other method in as exact detail as one who obtains almost perfect results with it. It is only natural that one will and should adhere to the method which gives him the best results.

In discussing the question of investigation of injury to the genito-urinary tract, the writer believes that the intravenous method of administration will be the one most extensively used. The reasons are several and obvious. In the first place, the patient is suffering more or less from shock, and vomiting usually occurs. The

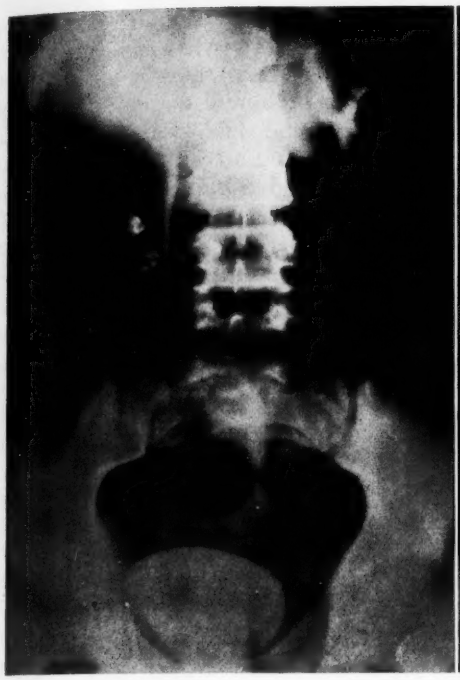

Fig. 5. Roentgenogram made 30 minutes after Figure 4.

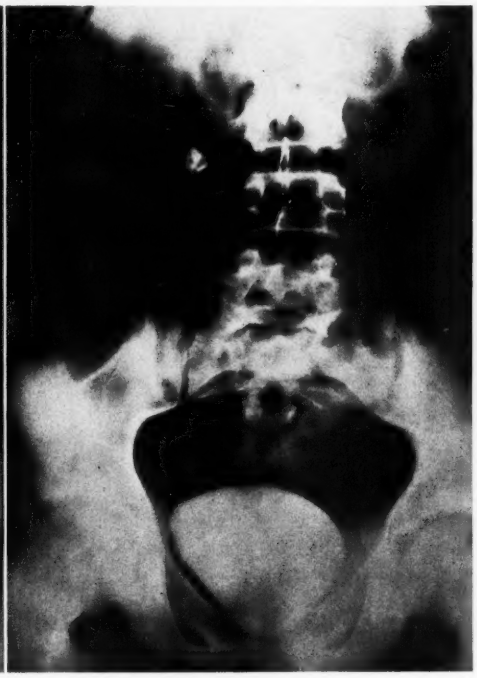

Fig. 6. Roentgenogram made 15 minutes after Figure 5.

former will react against the retrograde method and the latter against the oral. However, there are other reasons why the retrograde method should not be used in injury, especially in the upper genito-urinary tract.

Still, when injury to the bladder only is suspected, it is very easy and simple to inject some sodium iodide solution through the urethra and find out in a very short time whether or not a ruptured bladder exists. The writer had one such case in which the patient recovered without operation.

The intravenous method of administration to the genito-urinary tract enables one to obtain roentgenograms in five minutes: this is not possible at present with the oral administration of hippuran.

Injuries to the genito-urinary tract are often accompanied by ileus: this is another contra-indication to the oral method. The element of time is always a great factor in injuries, especially when they are internal.

The writer has seen thorotrast administered in injuries to the genito-urinary tract, but the wisdom of injecting that substance into the blood stream is questioned so strongly as to prohibit the use of it in its present form. There is a law in Austria forbidding its use anywhere in the country.

In examining patients with suspected injuries to the genito-urinary tract, it is important to remember that a certain condition may have been present prior to injury. This part of the history deserves special consideration. It cannot be presumed, although it is natural, that a person is absolutely normal up to the time of an injury: witness the conditions found in the spines examined for injury. These pre-existing pathologic entities may be aggravated by, and may have participated in, the injury, but beyond any question of doubt they existed before the trauma took place.

McKenna (1) has recently pointed out in a very excellent article the value of intravenous urography in injuries to the

Fig. 7. Gross specimen.

genito-urinary tract. He reports several cases of ruptured kidney diagnosed before and confirmed at operation.

The following case is reported by the writer:

A boy, aged 15, was sleighriding, March 1, 1934, when he collided with a parked automobile. He did not appear to be injured to any great extent, but on arriving at home a physician was summoned. There were no marks on the body except a slight abrasion over the left iliac crest. The boy was treated expectantly until it was seen that blood appeared in the urine. On the day following the injury he was taken to St. Joseph's Hospital, Carbondale, Pa., where an x-ray examination of the genito-urinary tract was requested.

The patient vomited several times; was very tender and rigid over the left side of the abdomen and pelvis. One of the physicians suspected a ruptured bladder—the tenderness over the left kidney was very moderate—notwithstanding the fact that it was twenty-four hours since the injury. Roentgenograms were made of the genito-urinary tract before the administration of any opaque material. These showed (Fig. 1) a considerable amount of gas in the bowel and neither kidney was visualized. A cluster of dense shadows was seen on the right side opposite the fourth lumbar vertebra. The line of the psoas muscle, however, could be plainly seen in its normal appearance on the right side; on the left side, it was distorted and pushed toward the mid-line.

Fifteen c.c. of neo-iopax was administered intravenously and roentgenograms made in five minutes (Fig. 2). Here we see the pelvis and calices of the right kidney and the right ureter. Note the distinction of the psoas muscle line on the right side, especially opposite the first and second lumbar vertebræ. The dense shadows previously described opposite the fourth lumbar vertebra apparently have no connection with the genito-urinary tract and were interpreted as being calcified glands in the abdomen. Note the obscured psoas muscle line on the left side, with no visualization of the left kidney or ureter.

Roentgenograms made at the end of twenty minutes (Fig. 3) showed the substance of the right kidney, with pelvis, calices, and ureter well outlined. Also note the difference in appearance of each psoas muscle line. The left kidney area is clearer and very irregularly outlined—no evidence of the left ureter.

At the end of thirty minutes (Fig. 4) practically the same appearance prevailed. Roentgenograms at the end of sixty minutes (Fig. 5) showed the right kidney, ureter, bladder, and the pelvic portion of the left ureter—this latter, I believe, was due

to back pressure from the bladder and not to any material which came from above on the same side. The bladder was not ruptured.

It was decided to wait until the bladder was quite distended in order to convince one of the physicians that it was not ruptured. Roentgenograms at seventy-five minutes (Fig. 6) showed the right kidney, part of the ureter, the bladder, and the pelvic portion of the left ureter, the latter much less distinct, however, than in the previous roentgenogram, and with no evidence of the ureter above the brim of the pelvis.

X-ray Findings.—Ruptured left kidney.

The patient was given pre-operative treatment and operated upon the following morning by Dr. Thomas P. Martin, assisted by Dr. Conarton, Dr. Kaufman, and Dr. La Conna. This was approximately forty hours after the injury (March 3, 1934). The patient's temperature was 100.6° F.; his pulse was 92; respirations, 24; hemoglobin, 80; red blood cells, 4,080,000; white blood cells, 18,500.

Urine.—Color, bloody; reaction, alkaline; sugar, negative; sp. gr., 1035; albumen + + + +.

Microscopic Examination.—Entire field contained red blood cells.

At operation the entire perinephric space contained blood and clots, the kidney was severely lacerated, being almost completely severed in several places (Fig. 7), and the left ureter was partially torn at its pelvic connection. The condition obviously necessitated removal. Drains, etc., were inserted. The boy had a very stormy time for about a week; however, he made a satisfactory recovery, and was discharged from the hospital March 16, 1934. The urine gradually cleared up so that, on discharge, it was practically normal.

This case is presented as one more addition to the list of injuries of the genito-urinary tract, already recorded, which were accurately diagnosed before operation.

REFERENCE

McKenna, Charles Morgan: Routine Use of Neo-skiodan in Suspected Injuries to the Genito-Urinary Tract. Jour. Am. Med. Assn., Feb. 24, 1934, **102,** 599–602.

EDITORIAL

LEON J. MENVILLE, M.D., *Editor* HOWARD P. DOUB, M.D., *Associate Editor*

THE LABORATORY—ITS GENESIS

The radiologist has been confronted with two obsessions, one the appellation of *laboratory*, the other the expression of *x-ray picture*. Both seemed reproachful. Of course, from the psychologic aspect of the radiologist these terms denote abject simplicity to such an extent that their repeated use seems to exert a derogatory influence on the minds of the lay people.

How frequently this was done, intentionally or unwittingly, is of no consequence—the end-results were the same.

One wonders how the designation of "laboratory" came to be applied to the office or the department of a radiologist. It was only a few years ago that the x-rays were discovered and they were discovered in a physics laboratory; is this the genesis of the term? Or, was it immediately applied because of the apparatus used, because of mechanization? If so, the use of an ophthalmoscope immediately places the office of an ophthalmologist in the category of a laboratory. Likewise, the use of a hammer, chisel, and saw, or a needle, thread, and scissors, by a surgeon, would classify the surgical department as a laboratory.

Because of peculiar circumstances that seemed to call for repeated clarification, the writer communicated with Dr. H. J. Holmquest, then Secretary of the Council on Physical Therapy of the American Medical Association, for assistance, which was generously given. He propounded the issue to the different members of the Council with the following responses:

G. M. MacKee, M.D.: "Regarding the definition of the word 'laboratory' as used by roentgenologists, I have given this some thought and I have been unable to think of a satisfactory definition. I wonder if it is necessary or even advisable to have such a definition. The word 'laboratory' is being used by roentgenologists instead of the word 'office,' and if it is continued to be used, it will undoubtedly become a standard word with a standard meaning or a reasonably definite meaning.

"As generally used in medicine, the word 'laboratory' indicates a place where experimental work is carried on or where diagnostic work is done or where preparations are made to be used therapeutically in another place. So far as I know, the word 'laboratory' has not been used for a place where patients are actually treated. According to this definition, it would be permissible to use the word 'laboratory' for a place where x-ray diagnostic work is done.

"There does not seem to be any real necessity for the word 'laboratory.' In an institution, the word 'department' would be used, and in private use, the word 'office' would seem to suffice. In this event, the word 'laboratory' would apply only to a place where experimental work is done with x-rays or radium.

"For obvious reasons, the word 'studio' is objectionable. It is probable that the word 'laboratory' will become a fixture and, if so, it might be well to indicate whether it is a diagnostic laboratory or a therapeutic laboratory and, of course, whether it is a radium laboratory or x-ray laboratory or both."

A. U. Desjardins, M.D.: "The word 'laboratory' is generally defined as a place devoted to experimental study in natural science or to testing, analyzing, or preparing drugs, chemicals, explosives, etc. The advisability of using this word at all in connection with the offices of a radiologist is seriously questioned. There is no better reason that the office and work rooms of a radiologist should be called a laboratory than that the office of any physician should be called a laboratory, because, in both cases, such rooms are not used chiefly for experimental or other allied purposes, but for the examination and treatment of human beings. Consequently, the use of this term does not appear consonant with the true meaning."

W. T. Bovie, Ph.D.: "The term 'laboratory' usually connotes a place where experiments are carried on, and therefore it would seem inadvisable to use it in referring to a clinic, for surely clinicians should not advertise that their

treatment has the slightest element of experimentation in it."

A. S. Warthin, M.D.: "The term 'laboratory' should not be used by radiologists as a designation for an office or establishment in which the use of roentgen rays or radium are employed only in a clinical way, for purposes of diagnosis or therapeutics. Such employment of x-rays or radium no more makes a 'laboratory' than the other methods employed by the physician. In the case of a public institution serving the profession at large for both diagnosis and treatment, the use of the term 'radiological laboratory' seems no more objectionable than 'clinical' or 'pathological laboratory' under similar conditions."

The following is a summation of Dr. H. J. Holmquest: The consensus of opinion of the members of the Council on Physical Therapy is that, since the word "laboratory" usually connotes a place where experiments are conducted for the purpose of scientific research, such name should not be used to designate the department of a hospital or the private office of a physician where radiological work of a diagnostic or a therapeutic character is carried on.

This correspondence took place in the Spring of 1927. What has happened in the last fifteen years?

Because the physicists, engineers, and chemists continue to perfect our apparatus, making possible a greater inclusion of diagnostic and therapeutic procedures, and because radiologists have conducted themselves with an earnest professional spirit, the terms "laboratory" and "pictures" should be tolerated as descriptive lay terms, condoned as corrupt medical terms, and gracefully accepted as simple expressions, which we *know* connote adjuncts to a service that has emerged from infantilism to reasonable and accepted maturity in two score years. But let *us* refrain from using them.

M. J. HUBENY, M.D.

ANNOUNCEMENTS

MID-SUMMER RADIOLOGICAL CONFERENCE[1]

IN THE ROCKY MOUNTAINS,

SPONSORED BY

THE DENVER RADIOLOGICAL CLUB

Wednesday evening, Aug. 28; Thursday, Aug. 29, and Friday, Aug. 30, 1935.

Place of Meeting.—Shirley-Savoy Hotel, Broadway at 17th St., Denver, Colo. All sessions in the Venetian Garden. (Hotel reservations should be requested in advance of the meeting.)

This Summer the Radiological Club of Denver is attempting a new venture in sponsoring a Radiological Conference for August 28, 29, and 30. The radiologists as well as other members of the medical profession in the Rocky Mountain region have felt the hardship in attempting to attend the various national meetings which are usually held at a considerable distance, and particularly in the East. A majority of the profession find it impossible to attend these meetings and, therefore, lose touch with the progress of medicine. It has been observed that every Summer there are a number of distinguished men who spend their vacations in Colorado. If given the opportunity these men are usually willing to present some of their recent work. For several years the Colorado Ophthalmological Society and the Colorado Society of Oto-laryngology have taken advantage of this situation in conducting a two-weeks course of teaching. These meetings have been very successful and have become well known.

The Denver Radiological Club will not offer any course of teaching but they will make it possible for the radiologists and the medical profession to meet and become acquainted with the work of some of the distinguished men in radiology. Among these guests will be Dr. B. H. Orndoff, Chicago, Secretary of the American College of Radiology; Dr. Edward Chamberlain, Philadelphia, Professor of Radiology at Temple University; Dr. J. M. Martin, Dallas, Texas, Professor of Radiology of Baylor University, and Dr. Henry S. Ullmann, Santa Barbara, California, Director of Cancer Research, Santa Barbara Cottage Hospital.

ORDER OF PROGRAM

Wednesday evening, Aug. 28

8:00 P.M. **Joint meeting with the Medical Society of the City and County of Denver.**

Guest Speakers:

W. Edward Chamberlain, B.S., M.D., Professor of Radiology, Temple University Medical School, Philadelphia.

[1] A complete program, including summary of all papers, will be mailed upon request to the Denver Radiological Club, Shirley-Savoy Hotel, Denver, Colo. No Registration Fee.

H. J. Ullmann, M.D., Director, Department of Cancer Research, Santa Barbara Cottage Hospital, Santa Barbara, Calif.

Thursday (morning session), Aug. 29

9:00 A.M. Address: "Welcome."
Frederick E. Diemer, M.D., *President*, The Denver Radiological Club.

9:15 A.M. **Symposium on Neoplastic Disease.**
Chairman: Harry Finney, M.D., F.A.C.S., Denver.

9:30 A.M. Treatment of Skin and Lip Malignancies.
H. J. Ullmann, M.D., Director, Department of Cancer Research, Santa Barbara Cottage Hospital, Santa Barbara, Calif.

10:15 A.M. Radiation Therapy in the Treatment of Carcinoma of the Intra-oral Cavity, Larynx, and Pharynx.
J. M. Martin, M.D., F.A.C.R., Professor of Radiology, Baylor University College of Medicine, Dallas, Texas.

11:00 A.M. Treatment of Advanced Malignancy.
Sanford Withers, M.D., Denver, Colo.

11:30 A.M. Discussion opened by
John M. Foster, Jr., M.D., F.A.C.S., Denver.

11:45 A.M. General Discussion.

12:30 P.M. Special Luncheon:
Talks by the Scientific Exhibitors.

1:00 P.M. Round Table Discussion on Problems in Radiation Therapy.
Sanford Withers, M.D., presiding. Present your therapy problems to be answered by our distinguished guests.

Thursday (afternoon session), Aug. 29

2:00 P.M. **Symposium on Gastro-intestinal Disease.**
Chairman: J. N. Hall, M.D., F.A.C.P., Denver, Professor Emeritus of Medicine, University of Colorado.

2:15 P.M. Further Discussion of the Relation of the Antrum and Cap to the Gall Bladder as Factors in Emptying the Gall Bladder.
Nathan B. Newcomer, M.D., and Elizabeth Newcomer, M.D., Denver.

2:45 P.M. Peptic Ulcer.
Ernst A. Schmidt, M.D., Denver.

3:15 P.M. Discussion opened by
T. D. Cunningham, B.S., M.D., F.A.C.P., Denver.

3:30 P.M. General Discussion.

4:00 P.M. **Biopsy and X-rays in the Diagnosis of Intra-uterine Conditions.**
Benjamin H. Orndoff, M.D., F.A.C.R., Chicago, Ill., Secretary, American College of Radiology.

4:45 P.M. Discussion opened by
Lyman W. Mason, M.D., Denver, President of the Denver Gynecological Society.

7:00 P.M. Informal Banquet ($2.00 per plate).
Frederick E. Diemer, M.D., presiding.
"Sunlight and Shadow."
Harmon P. Brandenburg, M.D., Denver, Hunter and Photographer.

Friday (morning session), Aug. 30

9:15 A.M. **Symposium on Pulmonary Disease.**
Chairman: Henry Sewall, M.D., Ph.D., D.Sc., Denver, Professor Emeritus of Medicine, University of Colorado.

9:30 A.M. Cystic Disease of the Lungs.
L. R. Moore, Major M.C., U. S. Army, Fitzsimons General Hospital, Denver.

10:00 A.M. X-ray Evidence of Infection in Region of Diaphragm.
Leonard G. Crosby, M.D., and Samuel B. Childs, M.D., Denver.

10:30 A.M. Inception of Adult Tuberculosis.
Kenneth D. A. Allen, M.D., Denver.

11:00 A.M. Differential Diagnosis between Pulmonary Tuberculosis and Non-tuberculous Disease of the Lungs.
W. W. Wasson, M.D., Denver.

11:30 A.M. Discussion opened by
Cicero L. Lincoln, M.D., F.A.C.P., Denver, President of the Denver Tuberculosis Society.

11:45 A.M. General Discussion.

12:30 P.M. Special Luncheon.
Short talks by the Commercial Exhibitors.

1:00 P.M. Round Table Discussion of Diagnostic Problems.
W. W. Wasson, M.D., presiding. Bring your diagnostic problems for discussion by distinguished guests.

Friday (afternoon session), Aug. 30

2:00 P.M. **Symposium on the Spine: Embryology, Anatomy, Anomalies, and Injuries.**

Chairman: Hamilton I. Barnard, M.D., F.A.C.S., Denver, Secretary of the Rocky Mountain Orthopedic Club.

2:15 P.M. Development of the Vertebræ and Intervertebral Discs in Their Relation to Pathology, Trauma, and Anomalies.
F. B. Stephenson, M.D., Denver.

2:45 P.M. Congenital Anomalies of the Spine.
John S. Bouslog, M.D., Denver.

3:30 P.M. The Radiologist's Part in the Problem of Low-back Pain.
W. Edward Chamberlain, B.S., M.D., Professor of Radiology, Temple University Medical School, Philadelphia.

4:15 P.M. Discussion opened by
George K. Cotton, M.D., Denver.

4:30 P.M. General Discussion.

4:45 P.M. What Conservation can Do in the Repair of Certain Misplaced Fractures.
Samuel B. Childs, M.D., Denver.

5:15 P.M. Discussion.

Scientific Exhibits

The Relation of the Antrum and Cap to the Gall Bladder.
Gastro-intestinal Ulcers and Diverticula.
Arthritis.
Pulmonary Metastasis.
Radiography with the Coolidge Tube in 1915.
The Pioneers of Radiology in Colorado.

Commercial Exhibits

Eastman Kodak Co., Medical Division, Rochester, N. Y.
General Electric X-ray Corporation, Chicago, Ill.
Paul Muckle, Representing The Standard X-ray Corporation, Denver, Colo.

ANNUAL MEETING

DETROIT, DECEMBER, 1935

The Executive Committee has invited Dr. H. Holthusen, of Hamburg, Germany, to deliver an address. Other guest speakers who are expected are:

Dr. Chevalier Jackson, of Philadelphia
Dr. Charles F. Geschickter, of Baltimore
Dr. H. C. Shepardson, Associate Professor of Medicine, University of California, San Francisco
Dr. J. B. Collip and Dr. Hector Mortimer, of McGill University, Montreal.

COMMUNICATIONS

MINNESOTA RADIOLOGICAL SOCIETY

The Minnesota Radiological Society held its annual meeting in connection with the Minnesota State Medical Association at Minneapolis, June 24, 1935. Dr. Percy Brown delivered an informal address on "Historical Reminiscences in the Development of Roentgenology" and following this gave a demonstration of the collection of x-ray tubes. The annual Carman Lecture was delivered by Dr. Percy Brown before the State Medical Association and his subject was, "The Inception of Fluoroscopy in the United States and Carman's Influence upon It."

New officers for the coming year were elected as follows: *President,* Eugene Leddy, M.D., Rochester; *Vice-president,* J. Richard Aurelius, M.D., St. Paul; *Secretary-Treasurer,* Leo G. Rigler, M.D., Minneapolis.

APPEAL TO THE ROENTGENOLOGISTS AND RADIOLOGISTS OF ALL NATIONS

The fortieth anniversary of the discovery of the roentgen rays comes in 1935 and we wish to fulfill a solemn obligation. We wish to commemorate with gratitude and to venerate all scientists, physicians, physicists, technicians, and nurses who were pioneers in roentgenology and radiology and who lost their lives for the welfare of mankind in the service of their science. These men and women from every nation joined their hands in a mighty dance of death, having paid for the loyalty to their profession and their love of mankind with excruciating suffering and painful death, while striving in common for knowledge and in emulation of the highest human ideals.

Lest we, who benefit from their scientific and medical accomplishments, should forget, we wish to immortalize them in "Strahlentherapie" by publishing a photograph and biography of each man and woman who died on the field of scientific honor in the battle against the diseases of mankind.

Each nation has made some contribution to this chapter of human heroism. We, therefore, sincerely request that roentgenologists and radiologists from every country send to the Editor of "Strahlentherapie" as soon as possible a photograph and short biographic sketch

(about two typewritten pages) of any of these pioneers in roentgenology or radiology whom they have known intimately.

Prof. Dr. HANS MEYER, Editor of "Strahlentherapie," 73 Parkallee, Bremen, Germany.

BOOK REVIEWS

LA ROENTGENTHÉRAPIE DES FIBROMYOMES DE L'UTÉRUS ET DES MÉTROPATHIES HÉMORRAGIQUES. By PAUL GIBERT. Preface by Dr. ANTOINE BÉCLÈRE, member of the Academy of Medicine. Published by Masson et Cie, Paris, 1935. Paper, pages 112, illustrations 10. Price, 18 fr.

This small book is an attempt to set forth the subject of roentgen therapy for fibromyoma of the uterus and for hemorrhagic metropathies. It is divided into chapters dealing with the clinical or diagnostic phases of the subject, the mode of action of roentgen rays, the relative advantages and disadvantages of roentgen therapy and radium treatment, indications and contra-indications, technic, incidents and accidents that may be observed during treatment, as well as the immediate and late effects of treatment, the influence of irradiation on gestation and heredity, the failures of roentgen therapy, the question of surgery after roentgen therapy, statistics, and conclusions.

This work fulfills its object admirably. The discussion of diagnosis and of the indications and contra-indications is especially good and is based on sound reasoning. In connection with the contra-indications, for instance, Gibert points out that too much has been made of infection as a contra-indication and that in many cases suitable treatment disposes of the infection as well as of the associated fibromyomatous process. As far as the technic of irradiation of fibromyomas is concerned, the methods described are those adopted by the French school under the leadership of the elder Béclère, and involve exposing the part to moderate quantitative doses of roentgen rays at intervals of a week for some time. In the light of present knowledge this seems wholly unnecessary because, as is well known, identical results can be obtained by giving the entire treatment within two or three days. Moreover, the incidents or accidents observed during treatment given within a few days are no greater than those described as incidental to the usual French method of treatment. This book is to be recommended to all those who wish up-to-date and reliable information on the subject, with, perhaps, the technical exception to which reference has been made.

CLINICAL PATHOLOGY OF THE JAWS, with a Histologic and Roentgen Study of Practical Cases. By KURT H. THOMA, D.M.D., and CHARLES A. BRACKETT, M.D., Professor of Oral Pathology in Harvard University, Oral Surgeon to the Brooks Hospital, Consulting Oral Surgeon to the New England Baptist Hospital, Consulting Oral Surgeon to the Tumor Clinic of the Beth Israel Hospital. A volume of 643 pages, 171 case histories, 423 figures, and 8 color plates. Published by Charles C. Thomas, Springfield, Ill., 1934. Price, $9.00.

This volume is an extremely valuable contribution to pathology and roentgenology of the jaws. Much of the material is presented by means of reports of cases encountered by the authors and by others, with excellent illustrations of roentgenograms and microscopic sections of tissue. Both the roentgenograms and the photomicrographs are extremely well reproduced. Although the book contains reports of many cases of the sort usually seen in this type of text, many unusual cases are also presented, such as cases of actinomycosis of the jaw. The colored photomicrographs of this condition are the best that this reviewer ever has seen. The classification of tumors of the jaw is based on clinical as well as microscopic examination of the tissue. Inflammatory lesions as well as neoplasms have been studied roentgenologically and microscopically, making a very interesting collection of material. The bibliography is voluminous, which makes the book of great value to the student.

Although the book should be of interest to the dentist who wishes collateral reading, it should also serve as a reference book for the roentgenologist and pathologist who is doing general work and who, at times, has to make diagnoses in a specialized field such as this. All in all, it is an extremely well prepared and illustrated volume, which deserves much commendation.

ABSTRACTS OF CURRENT LITERATURE

CONTENTS BY SUBJECT

Arteriography 243
Arthritis 243
Bone Diseases (diagnosis) 244
Cancer (diagnosis) 244
Cancer (therapy) 245
Colitis, Ulcerative 245
The Cranium 246
Dermatology 246
Esophagus (diagnosis) 247
Fever Therapy 247
Fistula 248
Gall Bladder (normal and pathologic) 248
Gastro-intestinal Tract (diagnosis) 248
Genito-urinary Tract (diagnosis) 249
Genito-urinary Tract (therapy) 250
Gynecology and Obstetrics 250
Heart and Vascular System 250
Hip Joint 251
Hodgkin's Disease (therapy) 251
Lead Poisoning 251
Leukemia 252
The Lungs 253
The Mediastinum 254
Parathyroid Glands 255
Peptic Ulcer 255
Radiation Effects 255
Roentgen-ray Burns and Injuries 256
Roentgen-ray Therapy 256
The Spine 256
The Stomach 256
Tuberculosis (pulmonary) 257
Tumors (diagnosis) 258
Tumors (therapy) 259
The Uterus 260

THE FOLLOWING ABSTRACTORS HAVE CONTRIBUTED TO THIS ISSUE

S. M. Atkins, M.D., of Waterbury, Conn.
J. E. Habbe, M.D., of Milwaukee, Wis.
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I. S. Trostler, M.D., of Chicago, Ill.

CONTENTS OF ABSTRACTS IN THIS ISSUE LISTED ALPHABETICALLY BY AUTHORS

Allen, Edgar V., and Camp, John D. Arteriography: A Roentgenographic Study of the Peripheral Arteries of the Living Subject Following Their Injection with a Radiopaque Substance 243

Archer, Vincent W., Blackford, Staige D., and Wissler, James. E. Pulmonary Manifestations in Human Tularemia: A Roentgenologic Study Based on 34 Unselected Cases ... 254

Aub, Joseph C. The Biochemical Behavior of Lead in the Body 251

Baker, Edgar C., and Lewis, John S., Jr. Comparison of the Urinary Tract in Pregnancy and Pelvic Tumors 249

Bargen, J. Arnold, and Leddy, Eugene T. Carcinoma of the Rectum: Some Causes for the Poor Prognosis 244

Bauer, Walter. What should a Patient with Arthritis Eat? 243

Bennett, A. E., and Keegan, J. J. Cerebral Neoplasms: The Diagnosis in the Absence of Generalized Intracranial Pressure Phenomena 246

Berg, George O., *with* Kling, David H. 256

Biondi, George C. Duodenorenal Fistula 248

Black, William C., and Faber, Harold K. Blood Vessel Tumor of the Spinal Cord in a Boy Aged Nine Years, with Special Reference to a New Diagnostic Syndrome 258

Blackford, Staige D. Pulmonary Manifestations in Human Tularemia: A Clinical Study Based on 35 Unselected Cases 254

Blackford, Staige D., *with* Archer, Vincent W., jt. auth. 254

Bloomfield, Arthur L. The Diagnosis of Early Cancerous Changes in Peptic Ulcer 244

Boggs, Robert, *with* Cutler, Elliott C., jt. auth. 248

Boynton, Ruth E. The Declining Death Rate from Tuberculosis in Children: An Analysis of Tuberculosis Deaths in Minnesota from 1915 to 1932 257

Brookes, Theodore P. Dislocation of the Cervical Spine: Some Predisposing Causes. 256

Camp, John D., *with* Allen, Edgar V., jt. auth.. 243

Coakley, Cornelius G., *with* Lenz, Maurice, jt. auth. 245

Cutler, Elliott C., and Boggs, Robert. Relation of Cystic Duct Obstruction to Deposition of Calcium in the Human Gall Bladder 248

Desjardins, Arthur U., Stuhler, Louis G., and Popp, Walter C. Fever Therapy for Gonococcic Infections 247

Desjardins, Arthur U. A Classification of Tumors from the Standpoint of Radiosensitiveness 259

Eller, Joseph Jordan. Roentgen Therapy in Dermatology 246

Faber, Harold K., *with* Black, William C., jt. auth. 258

Faccini, Bruno. The Roentgen Therapy of Tuberculous Lymphadenitis and Orchiepididymitis 256

Ferguson, Albert B., and Howorth, M. Beckett. Coxa Magna: A Condition of the Hip Related to Coxa Plana 251

Fine, M. James, and Jaso, James V. Silicosis and Primary Carcinoma of the Bronchus: Report of Case 254

Fray, Walter W. The Roentgenologic Diagnosis of Chronic Pulmonary Emphysema 253

Gardner, Clarence E., Jr., and Hart, Deryl. Enterogenous Cysts of the Duodenum: Report of a Case and Review of the Literature. 249

Garver, Hortense, *with* Kracke, Roy R., jt. auth. 252

Harrington, Francis E., Myers, J. Arthur, and Levine, Ida. Tuberculosis Among Employees of the Minneapolis Schools 257

Harris, William, *with* Rosenthal, Nathan, jt. auth. 252

Hart, Deryl, *with* Gardner, Clarence E., Jr., jt. auth. 249

Healy, William P. Radiation Therapy in Cancer of the Cervix 260

Hench, Philip S., Slocumb, Charles H., and Popp, Walter C. Fever Therapy: Results from Gonorrheal Arthritis, Chronic Infec-

tious (Atrophic) Arthritis, and Other Forms of "Rheumatism" 247
HOWARD, CAMPBELL. Observations on Encephalography 246
HOWORTH, M. BECKETT, *with* FERGUSON, ALBERT B., jt. auth. 251
HUHNER, MAX. Sterility and the X-rays 250
ILLICK, H. EARL, *with* STEWART, WILLIAM H., jt. auth. 257
JACKSON, CHEVALIER, and JACKSON, CHEVALIER L. Peroral Gastroscopy, Including Examination of the Supradiaphragmatic Stomach. 256
JACKSON, CHEVALIER L., *with* JACKSON, CHEVALIER, jt. auth. 256
JASO, JAMES V., *with* FINE, M. JAMES, jt. auth. .. 254
KEEGAN, J. J., *with* BENNETT, A. E., jt. auth. 246
KLING, DAVID H. Burns Produced by Radio Short Wave and Ultra-short Wave Therapy and Their Prevention 256
KORNBLUM, KARL, and OSMOND, LESLIE H. Mediastinitis 254
KOROL, EPHRAIM. Is It Empyema or Collapsed Lung? 254
KRACKE, ROY R., and GARVER, HORTENSE. The Differential Diagnosis of the Leukemic States, with Particular Reference to the Immature Cell Types 252
KRESS, LOUIS C. Bone Tumors and Irradiation. 259
LANDAUER, ROBERT S. Physical Aspects of Various Qualities of Radiation 255
LANZA, A. J. Epidemiology of Lead Poisoning .. 251
LEDDY, EUGENE T., *with* BARGEN, J. ARNOLD, jt. auth. 244
LENZ, MAURICE, COAKLEY, CORNELIUS G., and STOUT, ARTHUR PURDY. Roentgen Therapy of Epitheliomas of the Pharynx and Larynx. 245
LEVINE, IDA, *with* HARRINGTON, FRANCIS E., jt. auth. 257
LEWIS, JOHN S., Jr., *with* BAKER, EDGAR C., jt. auth. 249
LONG, ESMOND R. From Pathology to Epidemiology in Tuberculosis: Softening of the Caseous Tubercle and its Results 257
MCFETRIDGE, ELIZABETH M., *with* VEAL, J. ROSS, jt. auth. 243
MCPEAK, EDGAR M., *with* MERRITT, EDWIN A., jt. auth. 255
MACKIE, THOMAS T. Ulcerative Colitis: II. The Factor of Deficiency States 245
MACKIE, THOMAS T., and POUND, ROBERT E. Changes in the Gastro-intestinal Tract in Deficiency States, with Special Reference to the Small Intestine: A Roentgenologic and Clinical Study of 40 Cases 248
MARTIN, JAMES M., and MARTIN, CHARLES L. Modified "Coutard" Roentgen Therapy 259
MARTIN, CHARLES L., *with* MARTIN, JAMES M., jt. auth. 259
MERRITT, EDWIN A., and MCPEAK, EDGAR M. Roentgen Therapy of Hyperparathyroidism. 255
MYERS, J. ARTHUR, *with* HARRINGTON, FRANCIS E., jt. auth. 257
OSMOND, LESLIE H., *with* KORNBLUM, KARL jt. auth. 254
PFAHLER, GEORGE E., and VASTINE, JACOB H. The Roentgen Diagnosis and Treatment of Tumors of the Bladder: Their Serial Study with Pneumocystograms, Showing Results of Treatment by Irradiation 258
PFEIFFER, DAMON B., and WOOD, J. K.W. Cancer of the Transverse Colon in a Seven-year-old Boy 244
POPP, WALTER C., *with* DESJARDINS, ARTHUR U., jt. auth. 247
POPP, WALTER C., *with* HENCH, PHILIP S., jt. auth. 247
POUND, ROBERT E., *with* MACKIE, THOMAS T., jt. auth. 248
REBUSTELLO, EUGENIO. Radiographic Studies of the Vascularization of the Blood Supply of the Ileo-ceco-colic Region in Man 249
RIVERS, ANDREW B. Pain in Benign Ulcers of the Esophagus, Stomach, and Small Intestine 249
ROBBINS, CLARENCE L. Osteitis Fibrosa Cystica and Renal Calculi without Hypercalcemia .. 244
ROESLER, H. The Relation of the Shape of the Heart to the Shape of the Chest, with Special Reference to the Anteroposterior Dimension and the Morphology of Various Normal Heart Types: A Contribution to the Question of Accuracy of Ordinary Roentgenological Methods of Heart Measurement 250
ROSENTHAL, NATHAN, and HARRIS, WILLIAM. Leukemia: Its Diagnosis and Treatment ... 252
ROSH, RIEVA. Irradiation in the Treatment of Psoriasis 246
SLOCUMB, CHARLES H., *with* HENCH, PHILIP S., jt. auth. 247
STEINER, GEORG. An Aneurysm of the Pulmonary Artery 251
STEVENS, ALEXANDER R. Bilateral Urinary Calculi, with Special Reference to Therapeutic Problems 250
STEWART, WILLIAM H., and ILLICK, H. EARL. Roentgen Diagnosis of Carcinoma at the Cardia 257
STOUT, ARTHUR PURDY, *with* LENZ, MAURICE, jt. auth. 245
STUHLER, LOUIS G., *with* DESJARDINS, ARTHUR U., jt. auth. 247
TAYLOR, HENRY K. Interpretation of Roentgenograms in Pulmonary Tuberculosis 258
TROUT, HUGH H. The Treatment of Perforated "Peptic" Ulcers 255
UDVARDY, LADISLAUS. Exudates of the Pleura and Focal Pneumonia in Abdominal Diseases 254
VASTINE, JACOB H., *with* PFAHLER, GEORGE E., jt. auth. 258
VEAL, J. ROSS, and MCFETRIDGE, ELIZABETH M. Technical Considerations in Arteriography of the Extremities with Thorotrast 243
WARFIELD, LOUIS M. Results of X-ray Chest Examinations Among 2,500 Workers in a Heavy Industry 253
WHEATLEY, L. F. Lymphoblastoma with Paraplegia and Prolonged Irradiation 251
WINKELSTEIN, ASHER. Peptic Esophagitis: A New Clinical Entity 247
WISSLER, JAMES E., *with* VINCENT W., jt. auth. . 254
WOOD, J. K. W., *with* PFEIFFER, DAMON B., jt. auth. 244

ARTERIOGRAPHY

Technical Considerations in Arteriography of the Extremities with Thorotrast. J. Ross Veal and Elizabeth M. McFetridge. Am. Jour. Roentgenol. and Rad. Ther., July, 1934, **32,** 64–71.

A method has been devised which can be carried out by one person, and eliminates both incision and the tourniquet. The skin is anesthetized with 1 per cent procain, and the artery is punctured with a No. 18 needle attached to a syringe filled with the solution. As soon as the puncture is accomplished, pressure is made with the thumb over the artery just proximal to the site of injection, and is continued until all the solution has been introduced. It is then released and the exposure is made from three to six seconds later, depending on the distance between the site of injection and the location of the pathology. Thorotrast gave the authors the best results, 12 c.c. being sufficient for leg and foot, and 20 to include the lower thigh; 5 to 10 for the arm. If the subclavian is injected, a roentgenogram is made at the conclusion of the injection.

This work has been done on 150 cases including gangrene, embolic or thrombotic obstruction, angiospasm, arterio-venous aneurysm, and fibroblastoma of the sciatic nerve.

S. M. Atkins, M.D.

Arteriography: A Roentgenographic Study of the Peripheral Arteries of the Living Subject Following Their Injection with a Radiopaque Substance. Edgar V. Allen and John D. Camp. Jour. Am. Med. Assn., Feb. 23, 1935, **104,** 618–623.

In the extremities the arterial circulation as a whole may be adequate, even when some of its component parts are badly diseased. There are many methods for determining the sufficiency of the entire arterial circulation to extremities that leave little to be desired in determination of the efficiency of the arterial circulation as a whole. This situation is sharply in contrast to study of any component parts of the peripheral circulation. Arteries, except large ones, are not ordinarily visualized roentgenographically unless there is calcification in the walls, and even then no information can be gained regarding their caliber.

Arteriography was first carried out on living subjects in 1923. The ideal arteriographic substance is one which can be injected into an artery without producing pain, or immediate or delayed toxic effects and which is of good radiopacity in spite of the unavoidable dilution by the blood after injection. The authors used thorium dioxide sol (19 to 20 per cent by weight of thorium dioxide). In the interpretation of roentgenograms of the peripheral arteries, congenital variations from the usual formation of the vascular system, alterations in the lumen of arteries, as irregularities in contour, diminution of caliber, complete occlusion, and the presence or absence of collateral circulation, and its situation and extent. Normal variations in formation of the arterial system are many. The normal arteriogram is characterized by (1) smooth and uninterrupted contour of the lumens of the injected arteries; (2) direct course of these vessels, and (3) presence of no more than a minimum of collateral circulation. The size of the lumen varies in different subjects, and a small artery alone is not, primarily, evidence of disease.

The roentgenographic appearance of diseased arteries in thromboangitis obliterans, the development of collateral arteries in an attempt to compensate for occlusion of the main trunks, arteriosclerosis and aneurysm or arteriovenous fistula are discussed in detail. The chief value lies not in the direction of diagnosis but in that of pathogenesis. It gives information of inestimable value regarding the minutiæ of arterial disease, information which can be secured in no other way. The situation, extent, and nature of aneurysms, arteriovenous fistulæ, and arterial emboli can be determined accurately by arteriography. Whether or not the method will add information of value to knowledge of the pathogenesis of arthritis, hypertension and other conditions remains with the future to determine.

Charles G. Sutherland, M.D.

ARTHRITIS

What should a Patient with Arthritis Eat? Walter Bauer. Jour. Am. Med. Assn., Jan. 5, 1935, **104,** 1–6.

In this discussion the author states that no dietary can be adequately presented without stressing the fact that an accurate diagnosis is the first requisite. Some simple, workable classification should be followed by all. He divides his classification into those groups in which the origin is known and those in which the origin is unknown or uncertain. The first is subdivided into (1) the traumatic, which includes synovitis, loose bodies and cartilages, and sprains. In a second group he places those in which a bacterial agent is the known causative factor, tubercle bacillus, gonococcus, staphylococcus, streptococcus, pneumococcus, meningococcus, typhoid bacillus, dysentery organisms (amebic and bacillary), those due to the spirochete of syphilis, acquired and congenital (tenosynovitis syphilitica), influenza bacillus, and Brucella organisms. A third group includes the neuro-arthropathies (Charcot's joints), tabes dorsalis, syringomyelia, leprosy, etc.; the fourth, those considered as metabolic in origin, such as gout; the fifth, constitutional, as hemophilia and hysteria, and the sixth, the anaphylactic associated with serum sickness. With such a classification, one should be able to differentiate and properly diagnose the various arthritides. The arthritides of unknown origin, which embrace the degenerative (hypertrophic, osteo-arthritic, Type II arthritis); the proliferative (rheumatoid, atrophic, Type I, or chronic infectious arthritis), and rheumatic fever represent the types that have given rise to so much controversy concerning the diet in arthritis.

Degenerative arthritis is the result of "wear and tear" of increasing age and repeated trauma; the name adequately describes the cartilage changes that are

always observed in this type of joint disease. Simple weight reduction will often result in weight-bearing joints becoming symptom-free. Some of the marginal joint changes may be responsible for the symptoms; once these have become quiescent, the symptoms will disappear.

One of the most important things to be remembered concerning rheumatoid arthritis is that the disease is characterized by remissions and relapses. Remissions may last months or years. The diet for this group is discussed in detail. Treat the patient as a whole and observe the effect on the course of the disease. There is no specific diet for patients with arthritis of known origin, with the exception of gout.

C. G. SUTHERLAND, M.D.

BONE DISEASES (DIAGNOSIS)

Osteitis Fibrosa Cystica and Renal Calculi without Hypercalcemia. Clarence L. Robbins. Jour. Am. Med. Assn., Jan. 12, 1935, **104,** 117, 118.

The so-called metabolic criteria of hyperparathyroidism may be duplicated in conditions in which there is no evidence of hyperfunction of the parathyroids. Likewise, in proved cases of hyperparathyroidism the metabolic criteria may be absent.

The author reports a case of osteitis fibrosa cystica generalisata as an instance of probable hyperparathyroidism, fulfilling all the clinical and roentgenographic criteria of the condition with consistently normal concentrations of calcium and phosphorus in the serum. The patient was first admitted in 1922, when she was 48 years of age, for nephrectomy on the right side because of renal calculi and pyelonephritis. She was readmitted in 1933, when roentgen examination revealed a fracture through the middle third of the femur, with decalcification and multiple cysts in the distal fragment, producing marked distortion of trabeculations and expansion of the cortex. Similar cysts and osteoporosis were present in the right radius. The skull was the site of spotty rarefaction and thickening, rather suggesting Paget's disease. The twelfth thoracic and third lumbar vertebral bodies were markedly narrowed in their vertical diameters as the result of compression. In view of the osteoporosis, multiple cystic tumors, and renal calcification, hyperparathyroidism was diagnosed; the patient refused surgical intervention, and died shortly afterward. Necropsy was not obtainable.

C. G. SUTHERLAND, M.D.

CANCER (DIAGNOSIS)

Carcinoma of the Rectum: Some Causes for the Poor Prognosis. J. Arnold Bargen and Eugene T. Leddy. Jour. Am. Med. Assn., April 6, 1935, **104,** 1201–1203.

Many patients who have carcinoma of the rectum appear at the Mayo Clinic and elsewhere for examination when the local lesion is hopelessly inoperable. This also implies that many of these lesions are beyond even palliative irradiation when first seen. When it is recalled that carcinoma of the rectum causes definite and annoying symptoms, such as rectal bleeding, pain, constipation, and diarrhea, which get progressively worse, and that about 95 per cent of all these lesions are within reach of the examining finger, these facts are disheartening.

A careful analysis of the answers obtained from 200 patients led them to conlude that the poor prognosis of carcinoma of the rectum is the result of the following causes: (1) The frequent wasting of valuable time on the part of patients by self-diagnosis and self-treatment, and by regarding the symptoms as unimportant; (2) delay by the physician in making a digital examination of the rectum; (3) lack of knowledge, on the part of the patient, concerning the safety and satisfactory end-results of rectal surgery.

C. G. SUTHERLAND, M.D.

Cancer of the Transverse Colon in a Seven-year-old Boy. Damon B. Pfeiffer and J. K. W. Wood. Jour. Am. Med. Assn., April 6, 1935, **104,** 1227–1229.

Cases of carcinoma of the intestinal tract occurring in young persons must be looked on as extremely uncommon. Wainwright found only seven cases of cancer of the colon above the sigmoid in children. These authors tabulate eleven cases, all reported in children under 15 years of age.

They report a case of a boy, aged seven, in whom the barium enema was abruptly arrested about two inches above the level of the iliac crest in the descending colon. Surgical intervention because of the obstruction was followed by alkalosis, failing heart, and death. The pathologic examination revealed a fibroma showing superficial ulcerations; hemorrhages; extensive round-cell infiltration and several fields of misplaced, irregularly enlarged and distended intestinal glands which strongly suggested the presence of adenocarcinoma. Histological examination revealed a fibroma with adenocarcinomatous changes.

CHARLES G. SUTHERLAND, M.D.

The Diagnosis of Early Cancerous Changes in Peptic Ulcer. Arthur L. Bloomfield. Jour. Am. Med. Assn., April 6, 1935, **104,** 1197–1201.

The author discusses the various diagnostic methods and criteria that have long been considered valuable in the diagnosis of carcinoma of the stomach and concludes that none are reliable in the individual case. The only practical attitude to adopt, therefore, is to regard small, apparently innocent gastric ulcers as, in fact, benign until evidence to the contrary is weighty enough to arouse serious suspicions, and to accept the fact that a certain number of unavoidable tragedies will occur. They will occur in the future as they have in the past, not necessarily because physicians are careless but because they are helpless in the face of an insoluble problem of diagnosis.

C. G. SUTHERLAND, M.D.

CANCER (THERAPY)

Roentgen Therapy of Epitheliomas of the Pharynx and Larynx. Maurice Lenz, Cornelius G. Coakley, and Arthur Purdy Stout. Am. Jour. Roentgenol. and Rad. Ther., October, 1934, **32,** 500–507.

During 1931 and 1932, 31 epitheliomas of the larynx and pharynx were treated in the radiotherapy department of the Presbyterian Hospital, in New York City, initial exposure of the first case being given on Dec. 27, 1930, and the final treatment of the last case on Jan. 19, 1933. Only microscopically verified epitheliomas are included in this series.

It is considered important to improve to the maximum the oral hygiene of each case before beginning treatment. Extraction of carious teeth from a vigorously irradiated jaw frequently results in a late radionecrosis of bone.

Using a constant potential machine, the following factors were adopted: 200 K.V., 8 ma., 50 cm. target distance, 1.88 mm. copper and 1 mm. aluminum filter, size of field usually 6 × 8, 8 × 10, or 10 × 10 cm., average daily dose was 400 r without back-scattering to one field, administering 10 r per minute. The total dosage applied over two opposing fields varied from 2,800 to 4,800 r in successful cases, and from 2,400 to 5,000 r in the failures. The total dosage administered per patient varied from 5,600 to 9,400 r in the arrested, and from 7,500 to 13,000 in the non-arrested cases. (The larger dosage in the last-mentioned group was due to longer duration of treatment and a larger number of fields of irradiation.) In most cases any given field was exposed on alternate days, save Sundays and holidays, except in cases in which three portals of entry were used, when a given field was exposed every third day. Treatments were continued until a definite confluent pseudo-diphtheritic membrane covered the irradiated part of the mucosa ("radio-epithelitis"). This reaction disappeared two or three weeks later, leaving a slightly dry mucosa as the only residue. The membrane started to appear two or three weeks after the first treatment, but irradiation was continued until this membrane became pronounced and confluent. In the average successfully treated cases, radiation was continued over an interval of 30 days, and in the unsuccessful case, an average of 32.7 days. The radio-epidermitis of the irradiated skin occurred and healed during about the same interval as the mucosal reaction. The patients were ambulatory up to the time of the appearance of the mucous membrane reaction, then were hospitalized until it had subsided. Fluids are forced despite severe dysphagia, it being only occasionally necessary to resort to procto- or hypodermoclysis.

Thirty-one patients received this treatment; only 24 cases offered irreproachable clinical data for evaluation of the method. Of these, 11 of the 24 have shown no clinical evidence of recurrence for from nine months to two years since the last treatment, while in 13 cases this therapy failed to arrest the disease.

Microscopic classification of the tumor was as follows in the radiosensitive group: infrequence or absence of keratinization; few or no intercullular bridges; marked variation in the size and staining quality of cells and nuclei; numerous mitotic figures, and minimal inflammatory reaction. Radioresistant tumors showed the opposite microscopic picture. The doubtful group showed a mixture of radiosensitive and radioresistant characteristics.

Of the 13 failures, 10 were classed radioresistant microscopically, and of the 11 clinically arrested, nine were found to be radiosensitive and two mixed.

There were unilateral clinical metastases in the regional glands in six of the 11 apparently arrested cases, and in nine of the 13 failures. Tumors which are deeply infiltrated or badly infected do not respond well.

A few of these cases had tracheotomy performed before starting roentgen therapy. The tracheotomy tube was removed before and reinserted after each treatment.

Sticky, tenacious mucus is regularly encountered during Coutard therapy over the cervical areas, and dryness due to lack of saliva persists for months after treatment. The taste sensation is often lost and weight is regularly lost. However, the taste sensation usually returns gradually and the weight is regained in the responding cases.

J. E. Habbe, M.D.

COLITIS, ULCERATIVE

Ulcerative Colitis: II. The Factor of Deficiency States. Thomas T. Mackie. Jour. Am. Med. Assn., Jan. 19, 1935, **104,** 175–178.

Deficiency disease was encountered in 47 cases of chronic ulcerative colitis out of 75 consecutive cases (62.6 per cent) seen in hospital, dispensary, and private practice in New York City.

The objective changes find expression particularly in the mucous membranes of the mouth, in the skin, in changes in the blood chemistry, and in the associated anemia. Alterations in the mucous membrane of the tongue have been the most common of the abnormal manifestations. They appear to be among the earliest recognizable indications of deficiency disease. They present the features that are characteristic of sprue, pernicious anemia, and pellagra. Alteration in the texture of the skin has been the most common change observed.

Both the protein and the mineral metabolism of the body may be seriously disturbed in the advanced stages of chronic ulcerative colitis. Thirty-nine of the 75 cases showed significant grades of anemia. Twenty-nine of 37 cases studied roentgenographically showed significant changes in the small intestine. These frequently extended from the duodenum to the ileocecal junction. The normal mucosal pattern was distorted, as though the mucosa, and especially the valvulæ conniventes, were edematous. There was dilatation of individual coils and groups of coils without evidence of obstruction. There was disorganization

of normal motor function, with reduction of activity and uncoördinated muscular contraction. No evidence of ulceration of the small intestine was obtained. These changes were constantly present and most marked in patients with advanced grades of deficiency disease. Although the experimental evidence is striking, clinical experience has not supported the view that avitaminosis may operate as a primary cause of ulcerative colitis.

Studies have led to the belief that deficiency states play an important part in the mechanism of chronic ulcerative colitis. The lack of clinical signs of deprivation in a proportion of cases suggested that the factor of deficiency was secondary rather than primary. Deficiency disease is not to be regarded as an occasional complication of chronic ulcerative colitis. It seems more probable that it constitutes an essential part of the underlying mechanism.

C. G. SUTHERLAND, M.D.

THE CRANIUM

Observations on Encephalography. Campbell Howard. Am. Jour. Roentgenol. and Rad. Ther., September, 1934, **32,** 301–310.

Luminal is used in 4.5 grain amounts every hour, for two or three doses before the injection. This prevents the vomiting, although the headaches are not definitely affected. Views are taken in the erect and prone positions without the Bucky at 6 ft. distance. The vertical views are best for subarachnoid visualization and horizontal for the ventricles.

Combined enlargement of both ventricles and subarachnoid space is pathognomonic of cerebral atrophy or destruction.

The definite localization of frontal lobe tumors is of great aid to the surgeon. Subdural air is definitely associated with decreased intracranial pressure, and is found in epilepsy and atrophy from vascular lesions. It may be due to an arachnoidal defect around enlarged Pacchionian granulations. Observation of bone atrophy is very important in diagnosis of epilepsy or expanding intracranial lesions.

S. M. ATKINS, M.D.

Cerebral Neoplasms: The Diagnosis in the Absence of Generalized Intracranial Pressure Phenomena. A. E. Bennett and J. J. Keegan. Jour. Am. Med. Assn., Jan. 5, 1935, **104,** 10–16.

The authors deal with the diagnosis in the absence of generalized intracranial pressure phenomena, this classic cardinal symptom being lacking in from 15 to 30 per cent of large groups of patients with intracranial tumors, according to the studies of many observers. The principal cause of cranial hypertension is disturbance of the outflow of the cerebrospinal fluid. A tumor seems to raise intracranial tension very little until its growth interferes with the circulation of the cerebrospinal fluid. The location of the tumor is highly important in the production of early or late pressure phenomena. Midbrain and subtentorial tumors practically always show early pressure signs, while frontal lesions may develop to an unusual size without increased intracranial pressure.

The manometer in the authors' hands gives the most reliable and earliest guidance in the diagnosis of a pressure lesion. Such roentgenographic signs as evidence of local calcification, rarefaction of bone, increased diploic vessel marking, and shifting of the pineal shadow are valuable aids in diagnosis and localization. These occasionally give leads to diagnosis of tumor before neurologic signs are present.

It has been the practice of the authors to recommend encephalography in all adult epilepsies. The more frequently they resort to this examination the higher they find the percentage of organic causes for convulsions. With the aid of encephalography and experience, perhaps some of the malignant gliomas can safely be declared inoperable.

C. G. SUTHERLAND, M.D.

DERMATOLOGY

Roentgen Therapy in Dermatology. Joseph Jordan Eller. Am. Jour. Roentgenol. and Rad. Ther., August, 1934, **32,** 218–221.

X-rays are used in dermatologic practice in the following instances: (1) when it is desirable to epilate hair temporarily (tinea capitis, favus, sycosis, and nevus pilosis); (2) to reduce sebaceous gland activity (acne vulgaris and rosacea, and seborrhea); (3) to reduce sweat gland activity (hyperdrosis, bromidrosis, chromidrosis, pompholyx, and hydrocystoma); (4) to alter metabolism of the regional cells in order to render less favorable the growth of bacteria and fungi (in skin tuberculosis, fungus infections, furunculosis, etc.); (5) for the relief of itching, and (6) for caustic or destructive effect (skin malignancies).

The "skin unit" of unfiltered rays, that quantity just sufficient to cause temporary epilation, is given at 350 r. While there are, of course, individual variations in susceptibility, one may ordinarily administer 85 r weekly for three months to the face without immediate or ultimate reaction. Care is necessary in the treatment of inflammatory lesions because of the increased effect of the rays. Acute and chronic simple inflammatory dermatoses involving predominantly the epidermis may be given 42 to 85 r once weekly, while lesions involving the cutis with considerable infiltration and larger granulomas require more intensive treatment and the use of filters of from 1 to 3 mm. of aluminum.

J. E. HABBE, M.D.

Irradiation in the Treatment of Psoriasis. Rieva Rosh. Am. Jour. Roentgenol. and Rad. Ther., July, 1934, **32,** 82–86.

After discussing the various causes and methods of therapy that have been attempted, the method of treatment at Bellevue Hospital, New York City, is described. Since 1924, roentgen rays have been applied to the spine at those levels which correspond with the

nerve supply to the affected areas of the body. Since 1928, deep roentgen therapy has been used, the amount applied being from 75 to 100 per cent erythema dose per area. All patients were ambulatory. In most cases following treatment, the itching increased, to be soon followed by complete cessation of the symptom. Three weeks after treatment the color faded, the scales became loosed, and the surrounding skin infiltration was diminished.

In most cases a second series of treatments were given after from six to eight weeks. Complete disappearance of the lesions occurred in from three to six months after the last treatment; in some, a year. The cases treated were of many years' standing.

S. M. ATKINS, M.D.

ESOPHAGUS (DIAGNOSIS)

Peptic Esophagitis: A New Clinical Entity. Asher Winkelstein. Jour. Am. Med. Assn., March 16, 1935, **104,** 906–909.

The causes of esophagitis are usually given as: irritative (mechanical, thermal, and chemical irritants, including alcohol and tobacco); specific (syphilis, tuberculosis, and actinomycosis); secondary as a complication of (*a*) cardiospasm, (*b*) diverticula, or (*c*) neoplasms.

Recently the author has observed some patients with a type of esophagitis that does not seem to fit into this classification. The patients were all elderly men in whom, because of certain esophageal symptoms, carcinoma was suspected. The prolonged course of the disease and the results of biopsy were sufficient to exclude that diagnosis. Observations suggested the disease resulted from the irritant action on the mucosa of free hydrochloric acid and pepsin. The eroding gastric juice, rising into the lower part of the esophagus and held there by a mild spasm of the cardia, may injure the mucosa, made susceptible by age and the "ulcer constitution." Secondary infection may readily explain the more or less purulent nature of the inflammation. Association with duodenal, gastric, and preexisting peptic ulcer of the esophagus was noted in some of his cases.

CHARLES G. SUTHERLAND, M.D.

FEVER THERAPY

Fever Therapy for Gonococcic Infections. Arthur U. Desjardins, Louis G. Stuhler, and Walter C. Popp. Jour. Am. Med. Assn., March 16, 1935, **104,** 873–878.

In the past, many observers have noted an inhibitory effect of high temperature on gonococcic infections. Bacteriologists have long known that Neisseria gonorrhea can best be isolated and cultivated at a temperature of 37° C. (98.6° F.), and that the organism does not grow so well at temperatures greater than 38° C. (100.4° F.).

For a number of years artificial fever, induced by the injection of bacteria or protein substances, by general diathermy or by short wave radiations, the heating effect of which was fortuitously discovered by Whitney, who also realized its possible therapeutic value, has been used to treat syphilis of the nervous system, chronic arthritis and certain other conditions. During the last few years also the value of this method in treating acute gonococcic arthritis has been made increasingly clear. The rapid relief from pain and subsidence of inflammation obtained by thorough heating of the affected joints themselves, without general elevation of body temperature, is remarkable enough; but still more startling is the almost theatrical effect of increasing the general body temperature of such patients to between 41.1° C. (106° F.) and 41.7° C. (107° F.) and maintaining it at this level for five or more hours.

The average number of sessions of fever required to effect a cure was 5.4. The largest number of sessions required was twelve, in one case; this was owing to the fact that, during early sessions, an adequate degree of fever was not attained or was not maintained long enough. The lowest number of sessions of fever required for cure in any case was three. Later, an interval of only two days was allowed to intervene between sessions.

Fever therapy, especially for conditions requiring a high temperature, should be conducted in an institution where adequate facilities and trained personnel are available. It cannot be carried out in conjunction with other medical practice without increased risk.

CHARLES G. SUTHERLAND, M.D.

Fever Therapy: Results from Gonorrheal Arthritis, Chronic Infectious (Atrophic) Arthritis, and Other Forms of "Rheumatism." Philip S. Hench, Charles H. Slocumb, and Walter C. Popp. Jour. Am. Med. Assn., May 18, 1935, **104,** 1779–1790.

It has been observed clinically and experimentally that the lowering of body temperature diminishes the resistance of a host, human and otherwise, to certain bacterial infections. There is experimental evidence to support the contention that high temperatures exert a bactericidal and bacteriostatic effect on certain germs *vitro*. These observations provided the impetus for a trial of hyperpyrexia in the treatment of various diseases, including arthritis. Regardless of the method used, whether diathermy, radiothermy, hot baths, or heated cabinets, the resultant hyperthermia is characterized by more or less identical physiologic effects. These are reviewed in detail. Many of the reactions are of little or no importance from the standpoint of resultant discomfort or of relief. The benefits of fever therapy presumably arise from: (1) a direct bacteriolytic or bacteriostatic effect due to the influence of heat itself on bacteria (without necessarily implying formation of immune bodies); (2) an indirect bacteriolytic or bacteriostatic effect resulting from increasing formation or mobilization of immune bodies; (3) a local effect from vasodilation, providing an augmented blood supply to the inflamed tissues, and (4) a general effect from the heightened metabolism incident to fever. An arthritic patient may be helped by any one of these factors acting alone or in combination.

The following conditions have been considered to be contra-indications to fever therapy: advanced age, myocardial and renal insufficiency, marked hypotension, active tuberculosis, aortic aneurysm, rapidly progressing late neurosyphilis, and abnormal conditions of the skin which interfere with adequate sweating.

The results in gonorrheal arthritis are in striking contrast with those in non-specific infectious arthritis, the figures in the two groups being almost the converse of each other. Of 60 patients with chronic infectious arthritis, a total of 30 per cent received significant benefit and 70 per cent, little or no relief. About 90 per cent of patients with gonorrheal arthritis were essentially cured or markedly relieved.

CHARLES G. SUTHERLAND, M.D.

FISTULA

Duodenorenal Fistula. George C. Biondi. Jour. Am. Med. Assn., May 25, 1935, **104,** 1894–1897.

The author found but three cases of fistulous communication between the duodenum and the pelvis of the right kidney recorded in the entire medical literature. The first two were found at autopsy, a third recent case was demonstrated by urography. In the case reported the fistula was demonstrated by urography and on surgical intervention the finding was corroborated. A subsequent nephrectomy was done and the pathologic report on the tissue was tuberculosis of the kidney.

The author believes the ulcerative process originated in the duodenum because the gastro-intestinal complaint preceded the urinary disturbance by several months, because of the repeated failure to encounter any obstruction of the right renal tract, and because of lack of evidence of tuberculous changes on pyelography.

CHARLES G. SUTHERLAND, M.D.

GALL BLADDER (NORMAL AND PATHOLOGIC)

Relation of Cystic Duct Obstruction to Deposition of Calcium in the Human Gall Bladder. Elliott C. Cutler and Robert Boggs. Jour. Am. Med. Assn., April 6, 1935, **104,** 1226, 1227.

The importance of cystic duct obstruction on the deposition of calcium has been fairly well established, both clinically and experimentally. The authors report a case which they feel further substantiates the theory that obstruction of the cystic duct initiates the deposition of calcium and seems to represent an early stage in that process. The gross specimen obtained by cholecystectomy showed a mucosa of light pinkish-gray, and no area of erosion could be seen. The lumen contained 50 c.c. of an extraordinarily tenacious greenish-gray mucoid substance. Embedded in this material were nine large spherical white stones. These had a linear distribution extending from the fundus into the neck. The cystic duct was completely obstructed by a reddish-yellow stone of similar size. Throughout the fundal portion were scattered many small whitish stones roughly estimated at 200. The larger stones average 7 mm. in diameter and the smaller ones 2 millimeters. The cut surface of the stones was reddish-brown with radiating crystalline markings. The periphery of all the ones, with the exception of a few of the smaller ones and the one in the cystic duct, was formed by a very thin layer of chalky white material. Examination of the bile showed: calcium 28 mg. per 100 c.c.; cholesterol 750 mg., and bile salts 0. The absence of bile pigments is compatible with the views of Andrews and his co-workers that absence of bile salts is an important factor in cholesterol precipitation.

CHARLES G. SUTHERLAND, M.D.

GASTRO-INTESTINAL TRACT (DIAGNOSIS)

Changes in the Gastro-intestinal Tract in Deficiency States, with Special Reference to the Small Intestine: A Roentgenologic and Clinical Study of 40 Cases. Thomas T. Mackie and Robert E. Pound. Jour. Am. Med. Assn., Feb. 23, 1935, **104,** 613–618.

Deficiency disease may result from a defective dietary or from abnormal physiology of the gastro-intestinal tract. Defective absorption constitutes one of the outstanding features of sprue, and in certain cases has been shown to condition the development of the deficiency factors of the disease. The observation of advanced deficiency disease in several severe cases of ulcerative colitis led to a detailed clinical and roentgenologic investigation of a large group of cases of chronic ulcerative colitis. Evidence of deficiency states was found in 63 per cent of 75 cases studied. Consideration of possible etiologic factors suggested, among others, too rapid passage of the food constituents through the intestinal tract, or abnormalities of the small intestine producing defective absorption of the products of digestion.

Three cases of sprue and 37 cases of chronic ulcerative colitis were studied roentgenographically. Changes encountered in the small intestine were variation in the contour and size of the lumen, and alteration of the normal motor phenomena. The duodenum showed a thickening or widening of the circular markings in almost all severe cases, and in certain of the moderately severe ones. The lumen was frequently dilated and contained gas. The appearance resembled duodenitis except that no contracture or spasm was noted.

In the jejunem, the valvulæ conniventes were thickened and the spacings between them were widened. The normal mucosal pattern was distorted by the irregularities in the size of the valvulæ conniventes; in the partially filled segments it was often bizarre in appearance. The lumen was frequently dilated, and this dilatation was confined to local groups of coils or to isolated coils.

The changes in the ilium were quite similar to those noted in the jejunem. The outstanding feature of the rate of progress of the barium meal through the small

intestine is that the rapidity was not increased over the normal. The shortest emptying time was four hours. Twenty-four of the cases of chronic ulcerative colitis and the three cases of sprue showed a definite 24-hour barium residue in the colon. The barium enema in cases presenting the small intestinal changes has shown no constant relationship between these abnormalities and the extent and the severity of the lesions in the colon. In numerous instances, changes in the small intestine have been associated with a normal cecum and proximal colon.

The actual pathologic condition underlying the roentgenologic changes is not definite. The nature of the processes leading to these phenomena is obscure. The changes are those which could be produced by edema of the mucous membrane, disorganization of the normal motor activity, and reduction in tone of the intestinal musculature.

C. G. SUTHERLAND, M.D.

Enterogenous Cysts of the Duodenum: Report of a Case and Review of the Literature. Clarence E. Gardner, Jr., and Deryl Hart. Jour. Am. Med. Assn., May 18, 1935, **104,** 1809–1812.

Cysts and diverticula of the gastro-intestinal tract represent congenital abnormalities that are a problem to the clinician in diagnosis and to the surgeon in treatment.

Cysts of the duodenum have been noted in the literature only six times: two were in new-born children, one in a 3-weeks-old infant, one in an infant aged 19 days, one in a 3-months-old child, and the other in a 2-weeks-old female infant. In the case the authors report the patient was a girl 15 years of age.

Cysts which reduplicate all the layers of the normal intestine have their origin in defects of development of the intestinal tract. A cyst thus formed may occupy any position within the intestinal wall—submucous, intermuscular, or subserous—or any position around the intestinal wall—mesenteric, antimesenteric, or any intervening segment. A cyst on the mesenteric border, in addition, may lose its attachment to the intestine and occupy any position between the two layers of the mesentery. In none of the cases reported was the diagnosis made before operation. The most important diagnostic points are the presence of a tumor in the region of the duodenum and the signs and symptoms of duodenal obstruction. In those cases in which excision is not possible, the procedure of choice is permanent internal drainage of the cyst into the intestinal tract. An embryonic diverticulum is the probable origin of the cyst.

CHARLES G. SUTHERLAND, M.D.

Pain in Benign Ulcers of the Esophagus, Stomach, and Small Intestine. Andrew B. Rivers. Jour. Am. Med. Assn., Jan. 19, 1935, **104,** 169–173.

The clean-cut syndrome usually accepted as being diagnostic of peptic ulcer indicates an uncomplicated ulcer. When the pain of gastric ulcer shifts definitely to the left, slightly upward, or to the back, and when the pain of a duodenal ulcer is projected toward the right, upward through the region of the liver, or through to the back, or when the pain of a gastrojejunal ulcer extends downward, or through to the back, one can usually correctly assume deep penetration or partial perforation of such a lesion. The presence of two distinct separated areas of pain, especially if such pain is projected into two widely separated areas, frequently is indicative of two peptic lesions, such as an associated duodenal ulcer and gastrojejunal ulcer, or an associated gastric ulcer high on the lesser curvature, and a perforating duodenal ulcer. The situation of the pain of an obstructing ulcer, regardless of the situation of the lesion, is usually diffusely spread out over the epigastrium. Uncomplicated peptic ulcer probably indicates its presence as a visceral phenomenon, which asserts itself over the splanchnic nerves. The projecting pain of perforating peptic ulcers is probably the result of direct stimulation of the somatic nerves, with a relay of these impulses as pain into the peripheral or cutaneous branches of such nerves.

It is conceivable that the distortion of the approved ulcer syndrome in such instances is influenced by the accumulation of impulses of varying intensity over both the splanchnic plexuses of nerves and over the somatic nerves.

C. G. SUTHERLAND, M.D.

Radiographic Studies of the Vascularization of the Blood Supply of the Ileo-ceco-colic Region in Man. Eugenio Rebustello. Arch. di Radiol., 1934, **10,** 582.

The author here summarizes some observations he made on the blood supply of the ileo-ceco-colic region in 50 subjects, varying from full-term babies to adults of both sexes, and illustrates radiographically the usual distribution of the vessels and some of their anomalies.

E. T. LEDDY, M.D.

GENITO-URINARY TRACT (DIAGNOSIS)

Comparison of the Urinary Tract in Pregnancy and Pelvic Tumors. Edgar C. Baker and John S. Lewis, Jr. Jour. Am. Med. Assn., March 9, 1935, **104,** 812–815.

The study by intravenous dyes of the urinary tract in pregnancy meets ideal conditions. It is known that intravenous urography succeeds best when a certain degree of obstruction between the kidney and the bladder co-exists with a fair to good excretory function of the kidneys. Studies have revealed a high degree of dilatation of the upper urinary tract. This dilatation is more marked on the right side. It was early apparent that the position of the fetus had no effect on the dilatation. No real dilatation occurred until the uterus rose into the abdomen; it was more pronounced after the fourth month until close to term, when it appeared to subside slightly in some cases. At the third month, however, the upper tract on the right side showed better filling with the excreted dye than is usually seen in normal, non-pregnant patients. The stasis thus

demonstrated helps to explain the frequency of pyelitis or urinary infection in pregnancy.

Roentgenograms taken in the oblique positions showed clearly the relation of the sigmoid to the lower left ureter. The authors feel that the torsion of the uterus to the right is due to the sigmoid, and it seems a logical explanation of the cause of the rather marked right-sided preponderance of urinary dilatation. The sigmoid protects the left ureter and probably is the cause of the torsion of the uterus, with resultant increased pressure on the right ureter. Comparative studies of fibromas and ovarian cysts supported the mechanical obstructive theory.

CHARLES G. SUTHERLAND, M.D.

GENITO-URINARY TRACT (THERAPY)

Bilateral Urinary Calculi, with Special Reference to Therapeutic Problems. Alexander R. Stevens. Jour. Am. Med. Assn., April 13, 1935, **104,** 1289–1295.

The therapeutic problems peculiar to bilateral urinary calculi are not solved by the application of stated formulas. In clinical work one must secure data as complete as possible concerning the patient in general and his urinary tract in particular. The size and location of all calculi should be known, whether or not they obstruct, as well as the total renal function, the relative function of the two kidneys, and the presence or absence and degree of infection of both kidneys. There is no dependable method of dissolving calculi, but stones may pass spontaneously through the renal channels or be removed by operation.

Large, non-infected, non-obstructing, symptomless stag-horn calculi are usually left alone. Also, there is questionable advantage in trying to remove a large mass of non-obstructing, symptomless small stones occupying an entire kidney. There is no hurry in operating for small symptomless stones in a kidney even in the presence of low grade infection, whereas one does not dare wait long for the spontaneous passage of ureteral calculi associated with urinary infection. Relief of obstruction by a ureteral catheter, if possible, is usually a relatively harmless procedure; it may give temporary relief from symptoms and danger, may be followed by spontaneous passage of a calculus. Ureterotomy is one of the least dangerous major operations. Pyelotomy entails an added risk, and nephrotomy, particularly if extensive, is decidedly more dangerous. As a rule, ureterotomy and pyelotomy cause no immediate or remote decline of renal function, whereas in some cases nephrotomy has been followed by a decided, though perhaps transient, retention of non-protein nitrogen in the blood within a week or ten days. Secondary hemorrhages and acute kidney infections, when they do occur after operation, are usually encountered after nephrotomy incisions and not after pyelotomy. The more nearly complete urinary obstruction is, the more rapidly will kidney injury occur. The greater this injury, the less the return to function is to be anticipated following operation.

The data of 35 operative cases are reviewed, largely to illustrate the fallibility of commonly accepted rules. One should seek improvement of renal function primarily, and eventually control of infection and alleviation of symptoms.

CHARLES G. SUTHERLAND, M.D.

GYNECOLOGY AND OBSTETRICS

Sterility and the X-rays. Max Huhner. Jour. Am. Med. Assn., May 18, 1935, **104,** 1808, 1809.

X-rays in sufficient doses interfere with the spermatogenic function of the testicle or destroy it entirely. It must be recognized that different testicles react differently to the influence of the x-rays, some being more sensitive than others, so that what might be adequate protection in some cases would not at all be for others. The author reviews four positive cases and two doubtful ones, in which, in treatment for various conditions, dermatologists had produced sterility, and concludes that in some cases the testicles are so sensitive to the action of the x-rays that doses which are ordinarily considered harmless may cause sterility. The protective devices ordinarily employed to shield the testicles may not be adequate enough to prevent harm.

C. G. SUTHERLAND, M.D.

HEART AND VASCULAR SYSTEM

The Relation of the Shape of the Heart to the Shape of the Chest, with Special Reference to the Anteroposterior Dimension and the Morphology of Various Normal Heart Types: A Contribution to the Question of Accuracy of Ordinary Roentgenological Methods of Heart Measurement. H. Roesler. Am. Jour. Roentgenol. and Rad. Ther., October, 1934, **32,** 464–486.

The material presented in this article is based on orthodiagraphic measurements of the heart and chest in 150 normal individuals (without sternal depression), with special attention being directed to depth measurements and ratios in an effort to more accurately estimate cardiac volume and thereby make roentgenologic measurements more anatomically accurate and clinically effective.

Measurements for the adolescent and adult groups showed no appreciable differences. Ratios between heart diameters, chest diameters, and heart-chest ratios were very similar for the two sexes. In men, the average anteroposterior diameter was 8.7 cm., the normal range being 6.7 to 10.7; in women the average was 7.8 cm., with a normal variation from 6.3 to 9.6. Expressed in percentages, the ratio of heart depth to heart transverse diameter was 73.6 per cent for men, and 71.8 per cent for women. The ratio of heart depth to the oblique heart diameter was 67.4 per cent for men, and 64.1 per cent for women.

A close relationship was demonstrated to exist between the heart and chest, a flatter, broader, longer heart being found in the flat chest, and a deeper, narrower, shorter heart in a narrow chest.

Chest measurement ratios showed the average

anteroposterior diameter (sternum to vertebra) to be 41.5 per cent of the average transverse diameter.

When roentgen studies of the heart are made in one position only, the following possibilities may occur: two hearts of different volumes may give identical linear or area figures, or two hearts of equal volume may give different linear and area figures.

J. E. HABBE, M.D.

An Aneurysm of the Pulmonary Artery. Georg Steiner. Röntgenpraxis, March, 1935, **7,** 168–174.

Only a few cases of aneurysm of the pulmonary artery have been described. There are two types of these aneurysms: (1) multiple aneurysms, which are very rare, and (2) aneurysm of the conus, which is sometimes very hard to differentiate from diffuse widening due to emphysema, mitral stenosis, pneumothorax, etc. A few cases of aneurysm have been described in which there was not only involvement of the main artery, but also of the secondary branches. One such case is described in detail. The heart was markedly enlarged; the pulmonary conus was very prominent and beside it there was another semilunar shadow which pulsated; on oblique films there was a very definite aneurysm of the pulmonary artery. In this case an open duct, possibly combined with a septum defect, was the cause for the aneurysm, the author believes.

HANS W. HEFKE, M.D.

HIP JOINT

Coxa Magna: A Condition of the Hip Related to Coxa Plana. Albert B. Ferguson and M. Beckett Howorth. Jour. Am. Med. Assn., March 9, 1935, **104,** 808-812.

The common type of coxa plana is a nutritional disturbance of the upper femoral epiphysis due to a certain degree of interference with its circulation by sclerotic changes about the femoral neck. The sclerosis is the result of a preceding inflammation at the joint. When there is a circulatory disturbance of this kind not sufficiently severe to produce coxa plana, there may be enlargement of the femoral head and neck without other noteworthy changes. These cases present the clinical features of coxa plana but are characterized roentgenographically by enlargement of the femoral head and neck instead of by flattening and irregular ossification of the head. This condition is designated coxa magna.

The physical signs in the authors' cases resembled those of coxa plana. Roentgenographic examination revealed a broadening of the femoral head and neck, varying from one-sixteenth to five-sixteenths of an inch. The cartilaginous joint space was wide in four instances, normal in seven, and thin in two. The capsule of the joint appeared distended in six hips and not distended in seven. The broadening of the head and neck tended to increase for a varying time, while the other changes tended to revert to normal.

The treatment of coxa magna should be rest in bed without immobilization and removal of foci of infection.

CHARLES G. SUTHERLAND, M.D.

HODGKIN'S DISEASE (THERAPY)

Lymphoblastoma with Paraplegia and Prolonged Irradiation. L. F. Wheatley. Jour. Am. Med. Assn., Feb. 9, 1935, **104,** 460, 461.

This is a report of a case of lymphoblastoma (Hodgkin's type) in a girl first observed at the age of twelve. At the age of nine she had mumps in the left parotid region. A year later, an enlarged cervical gland was removed from the same side. Still another year later there was a recurrence, and a biopsy at this time was reported as showing tuberculosis. Routine examination at the sanitarium to which she was sent revealed a mediastinal tumor, and a biopsy at this time revealed the lesion to be a slow-growing lymphoblastoma; she was referred for radiation therapy. The mediastinal growth entirely disappeared following treatment at this time. Intermittent treatments controlled recurrences. After a six-year period she developed partial paraplegia. Heavy irradiation over the dorsal spine controlled the condition in that region for about one and a half years; she was apparently in a normal condition at the end of six months, when it returned, causing the death of the patient. An extradural mass was found at necropsy.

C. G. SUTHERLAND, M.D.

LEAD POISONING

Epidemiology of Lead Poisoning. A. J. Lanza. Jour. Am. Med. Assn., Jan. 12, 1935, **104,** 85–87.

Inhalation and ingestion are the two routes by which lead gets into the system, and the first is the more important. In the main, industrial poisoning is due to inhalation and non-industrial poisoning to ingestion. Water supplies conducted through lead pipes have been an important source of community poisoning. The greater the carbon dioxide content of the water, the more readily lead was carried into solution. Numerous instances have been reported of lead poisoning due to home fermenting and distilling of wines, beers, ciders, and similar beverages in utensils glazed with a lead compound. Lead was used to counterbalance a grinding wheel in a flour mill, with the result that the flour was impregnated with fine particles of metallic lead, poisoning a number of persons. Poisoning resulted from the metallic foil in which snuff was wrapped. The use of discarded storage battery cases for fuel resulted in several epidemics of lead poisoning. Lead poisoning from paint on verandas and railings where children played has been described. In Japan, the use of lead-containing toilet powders has caused widespread lead poisoning in both infants and mothers.

C. G. SUTHERLAND, M.D.

The Biochemical Behavior of Lead in the Body. Joseph C. Aub. Jour. Am. Med. Assn., Jan. 12, 1935, **104,** 87–90.

In the last ten years, a great deal of work has appeared on the subject of the biochemistry of lead. In regard to absorption, there is little new important evi-

dence. The experience in industry confirms the laboratory finding that lead which is inhaled is far more toxic than lead which is swallowed. The prevailing opinion has long been that lead is carried as an albuminate, but experiments and blood studies have offered convincing evidence that lead is precipitated in the bones as the very insoluble tertiary lead phosphate, and carried in the blood as the more soluble di-lead phosphate. In a chemical system as complicated as blood plasma, an equilibrium of several chemical compounds is not unreasonable. Any of these compounds might remain ionized and dispersed in the presence of plasma proteins. If larger quantities of lead are inhaled, swallowed, or injected, excretion does not maintain an equilibrium, and lead becomes stored. Once lead is absorbed, there is a characteristic distribution in tissues, which is approximately the same for inorganic, organic, or colloidal lead, no matter what the route of absorption. It is distributed throughout the viscera, but to the greatest extent in the liver, spleen, and kidneys, immediately following absorption. After a few days, however, it gradually collects almost entirely in the bones. The problem of treating lead poisoning is the problem of controlling the deposit and excretion of lead from this skeletal storehouse.

If rapid deleading is to be avoided, it is necessary simply to give a large calcium intake in the diet. This lowers the body's demands on calcium stores, and the only excretion of bone calcium (and lead) comes from the normal metabolism of the bones. Obviously, this is the method that should be used during any toxic lead episode.

After the episode has subsided, in the author's experience, a vigorous course of deleading is usually followed by a prompt recovery to normal health.

C. G. SUTHERLAND, M.D.

LEUKEMIA

The Differential Diagnosis of the Leukemic States, with Particular Reference to the Immature Cell Types. Roy R. Kracke and Hortense Garver. Jour. Am. Med. Assn., March 2, 1935, **104**, 697–702.

Until the second decade of the twentieth century there were recognized only two types of leukemia: myeloid, arising from the bone marrow, and lymphatic, having its origin in the lymphoid tissue. The recognition of a third type of leukemia involving the monocytic cells has engendered new ideas concerning the origin and classification of blood cells. All blood cells have their origin from the mesenchymal cell of the mesodermal layer in the embryo. From this point, opinions diverge in many directions.

It is virtually impossible to distinguish between the various types of leukoblasts with ordinary staining methods, or even with vital staining. Cases of chronic leukemias can be diagnosed easily, as well as acute forms, provided the total white cell count is definitely increased, with a preponderance of blast cells. The leukemic states in which the total number of white cells is normal, or below normal, offer considerable difficulty in diagnosis both clinically and hematologically and are apt to be confused with various leukopenic diseases.

The most reliable criterion for the diagnosis of any leukemia is a preponderance of immature cells regardless of the total number. Studies on a large number of cases of monocytic leukemia that are filed in the Hematological Registry indicate that the chief cell type has its origin in the bone marrow, and adds further evidence that monocytic leukemia is but an atypical phase of myelogenous leukemia.

CHARLES G. SUTHERLAND, M.D.

Leukemia: Its Diagnosis and Treatment. Nathan Rosenthal and William Harris. Jour. Am. Med. Assn., March 2, 1935, **104**, 702–706.

Leukemia has heretofore been regarded as a disorder characterized by a persistent increase in the number of white blood cells. According to the present concept of the disease, however, an increase in the number of white cells is not an essential diagnostic factor.

The authors classify 455 cases seen in hospital and private practice over a period of fifteen years and discuss the blood picture, symptomatic variations, and differential diagnosis. A typical case of leukemia, either acute or chronic, is usually differentiated by the presence of an increased number of white blood cells as well as mature or premature leukocytes. However, difficulty in diagnosis may be encountered in cases of leukopenic leukemia in which the number of leukocytes is normal or profoundly reduced. Such cases, when admitted to the hospital, are sometimes diagnosed as pernicious anemia, purpura hemorrhagica, agranulocytosis, subacute endocarditis, splenic anemia, or other disorders.

Radiotherapy is the most satisfactory method of treatment, of greatest therapeutic value in chronic myeloid and chronic lymphoid leukemia. Radium, in the form of surface application or packs, is used only in the event that roentgen therapy is not available, or in patients who cannot be moved from their homes.

The marked radiosensitivity of leukemic tissue and the lability of the blood count necessitate extreme caution. In general, marked reactions should be avoided, and rapid regressions of leukemic deposits should not be sought. In the authors' series the areas treated were the spleen in myeloid cases, and palpable lymph nodes and spleen in the lymphoid cases. Occasionally the long bones or the flat bones were irradiated, but the response appeared to be somewhat slower. The effect of roentgen treatment is measured by the degree of symptomatic improvement. In favorable cases there is a rise in the hemoglobin and an increase in the red blood cells, a response that occurs more rapidly in myeloid cases. In lymphoid leukemias the improvement is not so marked. After the first series of roentgen treatments the blood picture may return to normal, particularly in chronic forms, and it may remain so for a variable period—from a few weeks to nine months. The symptomatic improvement, however, may be of longer duration. Additional treatment in their cases proved less successful. In time, patients

become more resistant to the treatment and, as the disease progresses, do not tolerate it well.

CHARLES G. SUTHERLAND, M.D.

THE LUNGS

Results of X-ray Chest Examinations Among 2,500 Workers in a Heavy Industry. Louis M. Warfield. Industrial Medicine, June, 1935, **4**, 302–306.

Twenty-five hundred workers in a large industy, located in a small city near Milwaukee, Wisconsin, which employs 3,500 men and a few women, recently equipped a roentgen department and began a study of the chests of its employees. The plant has two foundries, machine shops, etc.

It was decided that a single postero-anterior film taken at 5 feet, 75 to 80 K.V., 100 ma., $^1/_{10}$ second exposure would meet most requirements. If flat films proved inadequate, stereo sets were made.

In the two foundries 691 chests were examined, the men ranging from 18 to 80 years. Scattered cases of silicosis were found in several of the machine shops, but in every case the past occupational history revealed that the individual had worked in copper or iron mines for from 10 to 37 years. The silicosis cases found among the 2,500 examined (including 113 women) were found in the foundries, boiler shops, brass foundry, and forge shop. The cases outside of the foundries were found to be very mild and not of any significance.

After examining over 4,000 chest films during the last 18 months, the writer feels that the flat film is quite satisfactory.

The most striking comparison shown in these examinations is the evident difference between the lesions produced by silica inhalation in the foundry workers and in granite-cutters. The only comparable conglomerate lesions were those found in sand-blasters and granite-cutters. *There were none of the massive infiltrations seen among the 2,500 workers of this series.* [Abstractor's italics.]

It is exceedingly doubtful if the most expert roentgenologist can make a certain diagnosis of the so-called first stage silicosis even if he has the occupational history of the subject of the examination. [Abstractor agrees with this and says "Amen" to it.] It is well recognized that hilum shadows are so variable in size and density in normal lungs that opinions based upon hilum appearances are likely to be incorrect. The added criterion of the first stage, namely, "more fibrosis than normal," is also a limber reed to hold up an opinion.

The only case of active tuberculosis seen was in a man 38 years old who applied for work in the foundry and who had been a core worker in other foundries for 18 years. He showed no evidence of silicosis. With pulmonary tuberculosis so widespread and with evidence of childhood healed infection in 100 per cent in this study, it seems strange that none of the 691 foundry workers examined showed active tuberculosis. There is no evidence that tuberculosis in the presence of mild or moderately severe silicosis heals as it usually does in non-silicotic lungs.

This raises the question of the accuracy of the widely accepted view that silicosis activates tuberculosis. Animal experiments seem quite conclusive, but we must bear in mind that, however carefully animal experiments are performed, conclusions drawn from these experiments can be true only for the animal treated in that particular way. One has no right to conclude that because animals react under artificially created conditions, humans will react similarly under natural and widely different conditions.

A further interesting observation is that increased linear markings and beading of the linear markings were not found in the silicotic lungs but in the lungs in which healed calcified nodules, presumably due to tuberculosis, were present. Silicosis is probably not the cause of the increased linear markings, but tuberculosis is.

Individual predisposition plays an important part. One 76-year-old iron moulder (for 52 years) showed very mild silicotic lesions. Another (56 years old), who had worked in Michigan iron mines for 25 years and afterwards in a foundry for seven years, had lungs which showed only moderate nodular lesions. Another (51 years old) had been a moulder for 34 years, with no lung signs of silicosis. A man of 47 has been a chipper of castings for 29 years, with lungs normal. One man, aged 80, a chipper for 22 years, had no lesions.

On the other hand, four men between 20 and 39, all of whom had begun work before they were 18, showed very early signs of silicosis.

Of the 2,500 films examined, 2,355 were negative for silicosis. Of the 691 foundry workers, 562 were negative. Among the 2,500, there was one case of complete situs transversus, and three cases of eventration of the left leaf of the diaphragm. There was one case of bronchiectasis and one individual had a mass in the hilum which was thought to be malignant.

Examination of 2,500 flat films showed 527 men with some abnormal findings, the great majority of which were compatible with good health and ability to work. Of 691 foundry workers, 129 had demonstrable silicosis.

I. S. TROSTLER, M.D.

The Roentgenologic Diagnosis of Chronic Pulmonary Emphysema. Walter W. Fray. Am. Jour. Roentgenol. and Rad. Ther., July, 1934, **32**, 11–22.

The roentgenologic findings in emphysema may vary considerably. Signs which have been considered of value are : (1) increased space between the heart and sternum, which remains essentially unaltered during inspiration and expiration; (2) low flattened diaphragm with limited mobility; (3) increased prominence of pulmonary marking in the peripheral lung zone; (4) general increase in brilliancy of the lung-fields; (5) diaphragmatic folds, and (6) irregular dilatations of bronchi after lipiodol injections. The writer made careful comparative studies of the fluoroscopic and radiographic findings of 52 normal and 52 emphysematous individuals, the radiographic data being obtained from routine postero-anterior and left anterior oblique films. The important roentgenoscopic findings

are: (1) unchanged radiolucency of lung-fields during the respiratory cycle; (2) clear definition of the diaphragm at the end of maximum expiration. The roentgenographic findings are more numerous and variable. One of the most reliable is that of a low "thoracic index" (a figure obtained from the two above-mentioned films, by dividing the transverse diameter of the chest at the level of the base of the heart on the postero-anterior film by the transverse diameter on the left oblique film). In the normal, this ratio varies from 0.96 to 1.26 (average 1.10), while in emphysema the range was from 0.85 to 1.07 (average 0.96). Thoracic flaring is another fairly constant sign. Low position of the diaphragm, increased brilliancy of the lung-fields, and peripheral lung markings were not found to be reliable signs in this series of cases.

J. E. HABBE, M.D.

Pulmonary Manifestations in Human Tularemia: A Clinical Study Based on 35 Unselected Cases. Staige D. Blackford. Jour. Am. Med. Assn., March 16, 1935, **104,** 891–895.

Pulmonary Manifestations in Human Tularemia: A Roentgenologic Study Based on 34 Unselected Cases. Vincent W. Archer, Staige D. Blackford, and James E. Wissler. Jour. Am. Med. Assn., March 16, 1935, **104,** 895–898.

Tularemia affected the thoracic viscera in a high percentage of cases which came to necropsy; this study demonstrates that pleuropulmonary infections are frequent in patients who recover from the disease. Clinical methods detected lung or pleural involvement in approximately half of this unselected series, and roentgenograms revealed abnormalities in the chest in more than 90 per cent of their cases.

Chest films were taken in 34 of 35 cases at some time subsequent to the inoculation, in 18 patients during the active stage of the disease, eight of these returning after recovery for further roentgen examination. Roentgenograms after recovery were made in 16 of the remaining cases. Seven showed pulmonary consolidation, seven peribronchial thickening, three pleural effusion, and one nodular infiltration. The residual changes were: (1) increased fibrosis, and (2) an apparent increase in calcification.

CHARLES G. SUTHERLAND, M.D.

Is it Empyema or Collapsed Lung? Ephraim Korol. Am. Jour. Roentgenol. and Rad. Ther., August, 1934, **32,** 198–205.

The roentgenologic recognition of the development of an empyema occurring in the course of a chronic lung disease presents great difficulties because of fibrosis, atelectasis, and adhesions usually being present. Five cases are presented to illustrate the great likelihood of suggestive clinical and roentgenologic findings not being confirmed by operative or postmortem studies.

Two special radiographic diagnostic procedures are recommended for this type of case. In cases in which the suspected empyema or atelectasis is apical, roentgenograms should be made in deep inspiration and deep expiration. If the density is caused by fluid, there is no change in its appearance on these two films; if caused by atelectasis, it enlarges and "brightens up" due to a relative inflation with forced expiration (Kreutzfuch's phenomenon). If the density is at the base, a special supplementary film should be taken, with the subject lying on the good side, for areas of atelectasis are generally inflated in the higher lung.

J. E. HABBE, M.D.

Exudates of the Pleura and Focal Pneumonias in Abdominal Diseases. Ladislaus Udvardy. Röntgenpraxis, December, 1934, **6,** 785–792.

Disease processes in the abdomen may and often do lead to secondary changes in the base of the lungs and in the pleura. The diaphragm has many lymphatics which allow the migration of such processes from the abdomen into the chest. If an infection spreads from the abdomen into the chest, the costophrenic angle is usually obliterated by a small exudate and there are intensive, broad, long, horizontal bands visible in roentgenograms of the chest which are usually situated just above the diaphragm. These shadows represent a fibrous pleurisy. The pleuritic changes are almost always on the same side as the primary disease in the abdomen. Processes in the mid-abdomen (as, for instance, a pancreatitis) may cause pleuritic symptoms on both sides. Cases with typical roentgenologic symptoms are described: carcinoma of the ovary, carcinoma of the cecum, purulent cholecystitis, chronic abscess of the gall bladder, advanced cirrhosis of the liver, appendiceal abscess, and pancreatitis. Sometimes there is not only a transmitted pleurisy, but also bronchopneumonia. The horizontal pleuritic thickening disappears after the primary disease in the abdomen has healed.

HANS W. HEFKE, M.D.

Silicosis and Primary Carcinoma of the Bronchus: Report of Case. M. James Fine and James V. Jaso. Jour. Am. Med. Assn., Jan. 5, 1935, **104,** 40–43.

This is a case report concerned with chalicosis or silicosis. The authors subdivide pneumonoconiosis into: (1) anthracosis (due to the inhalation of coal dust); (2) siderosis (following the inhalation of iron and steel dust, and (3) chalicosis or silicosis (resulting from the inhalation of stone dust).

The patient was referred to the chest clinic with a diagnosis of advanced pulmonary tuberculosis. He had been a stone cutter for 20 years and had abandoned his work three years before because of increasing dyspnea. On admission to the hospital, the dyspnea was severe enough to require oxygen therapy. The patient died within two months. Necropsy revealed a co-existent carcinoma and silicosis.

C. G. SUTHERLAND, M.D.

THE MEDIASTINUM

Mediastinitis. Karl Kornblum and Leslie H. Osmond. Am. Jour. Roentgenol. and Rad. Ther., July, 1934, **32,** 23–42.

This diagnosis is difficult to make and only by the

combination of the clinical and roentgenologic findings can any degree of accuracy be reached. The disease is either inflammatory or neoplastic in nature.

Anatomically, the mediastinum communicates with the neck, retroperitoneal tissues, areolar tissue between the parietal pleura and sides of vertebræ, the space between the ribs and parietal pleura anteriorly, lungs and region between pleura and lung. Thus complications of various sorts may arise, and the infection spread from the mediastinum to the communicating regions and *vice versa*.

Usually, the condition is secondary, and by extension, although also from trauma, metastasis, and hematogenous spread. It may be acute or chronic, diffuse or localized, suppurative or non-suppurative. The latter is rarely recognized. The acute suppurative may follow a foreign body in the esophagus, the trachea or bronchi. Chronic mediastinitis is not uncommon. It frequently follows pericarditis, and results in adhesions between the mediastinum and pericardium. The most common cause is tuberculosis; syphilis, actinomycosis, and Hodgkin's also occur.

The cardinal symptoms are cough, pain, and dyspnea, but many others may be present; in some, especially chronic, the symptoms may be absent.

Roentgen examination is the best means of detecting the disease, although considerable difficulty is encountered. Usually there is a bilateral general widening of the mediastinum. In the acute localized suppurative form, a fluid level, if examination is made in a sitting position, may be seen in addition to the general widening. In the chronic, the contour is somewhat irregular and indistinct, and the trachea and bronchi may be distorted. Evidence of compression of the lung is usually present. The esophagus may show changes in its contour. Fluoroscopically, the heart is fixed in both phases of respiration, at times an upward tug of it being present on deep inspiration. The localized tuberculous form may show calcification.

S. M. Atkins, M.D.

PARATHYROID GLANDS

Roentgen Therapy of Hyperparathyroidism. Edwin A. Merritt and Edgar M. McPeak. Am. Jour. Roentgenol. and Rad. Ther., July, 1934, **32,** 72–81.

Osteitis fibrosa cystica (von Recklinghausen's disease) is now known to be caused by hyperparathyroidism. Such other bone diseases as Paget's ankylosing polyarthritis, multiple myeloma, and giant-cell tumor may also be of endocrine origin, although apparently not due to pure parathyroid dysfunction.

von Recklinghausen's disease occurs most commonly in females between the ages of 30 and 60 years. The cardinal symptoms are pain, weakness, weight loss, loss of appetite, and constipation. Occasionally there is elevation of temperature, and postural abnormalities are the rule in late cases. Blood calcium is usually elevated, and serum inorganic phosphorus decreased with increase of both calcium and phosphorus in the urine, hence renal calculi are frequently found. The multiple areas of cystic thinning of the bones commonly involve the metaphyseal regions of long tubular bones, while the vertebral bodies show compression fractures.

While there are a number of cases on record of surgical cure of one or more of the parathyroid glands, there is no satisfactory medical treatment. The authors recommend radiation therapy over the parathyroids as a more conservative procedure, which may nevertheless prove equally as effective, particularly in view of the wide variation in the amount and location of the parathyroid tissue. Six cases of cystic bone disease with findings more or less characteristic of hyperparathyroidism have been treated by conservative radiation (using 140,000 volts, 6 mm. Al filtration, 10 × 15 cm. fields, exposures of 240 r per field measured in air, each of four fields including either side of the neck anteriorly, the upper thorax anteriorly, and the neck posteriorly being exposed at intervals of three weeks between each series), with cure or definite improvement being obtained in every case. The authors have never encountered personally or found in the literature a case of tetany following roentgen therapy for any disease process in the neck, and, therefore, feel that the treatment can be recommended as being entirely free of danger and as being on the same rational basis as that of ovarian, pituitary, thyroid, or other internal glandular dysfunctions.

J. E. Habbe, M.D.

PEPTIC ULCER

The Treatment of Perforated "Peptic" Ulcers. Hugh H. Trout. Jour. Am. Med. Assn., Jan. 5, 1935, **104,** 6–9.

This paper deals only with the acute perforating ulcer that demands immediate operation. Surgery offers the best hope of recovery. The type of closure is a somewhat different problem in each individual case. Drainage of the peritoneal cavity should be avoided if possible. Continuous gastric suction through a nasal tube has decreased the indications for an immediate gastro-enterostomy. Partial gastric resection is the operation of choice in those cases of perforation of the stomach or duodenum which are associated with massive hemorrhage.

C. G. Sutherland, M.D.

RADIATION EFFECTS

Physical Aspects of Various Qualities of Radiation. Robert S. Landauer. Am. Jour. Roentgenol. and Rad. Ther., August, 1934, **32,** 235–238.

Draper's fundamental law of photo-chemistry states that only that radiation which is absorbed produces any chemical action. As a corollary, it can be stated that only that radiation which is absorbed produces any biologic action. Furthermore, it can be assumed

that in cases in which radiation is beneficial to tissue, the greater the quantity of radiation absorbed, the greater the beneficial effect.

The major premise of this article is that regardless of how "hard" the radiation, it is impossible to "shoot through" a lesion, and, conversely, the harder the radiation the larger the absorbed depth dose. Landauer points out that x-ray intensity measuring instruments, whether used to determine surface or depth doses, do not measure that radiation "passing through," but do measure the dose absorbed at the measured depth. Some workers would explain the difference in the erythema dose measured in roentgens for different qualities of radiation entirely on the difference in rate of administration, while others believe that under certain conditions the effects of equal quantities of radiation of different wave lengths are different. Landauer has compared the roentgen-per-minute output of the 200 K.V. mechanically rectified transformer, the 600 K.V. transformer, and the radium bomb, and their respective depth doses, and has found the 600 K.V. transformer to give the most efficient depth dose in the most economic interval of time.

J. E. Habbe, M.D.

ROENTGEN-RAY BURNS AND INJURIES

Burns Produced by Radio Short Wave and Ultra-short Wave Therapy and Their Prevention. David H. Kling. With an Additional Case Report of a Severe Burn by George O. Berg. Jour. Am. Med. Assn., June 1, 1935, **104,** 1981–1984.

Abstracts of the histories of six cases in which burns developed in the course of radio short wave and ultra-short wave therapy are given. Three had second degree burns and three showed third degree burns, with extensive destruction eventually necessitating skin grafts. In experimental work burns were produced in rats, ranging from edema to gangrene and loss of ears, limbs, and tails.

The widely circulated assumption that the use of condenser electrodes in short and ultra-short wave therapy excludes burns and simplifies the technic is a dangerous fallacy. Sufficient energy, proper electrodes and distance from the skin, absorption of perspiration, and constant control of patient and apparatus are imperative in order to prevent damage and derive the benefits of short and ultra-short wave therapy.

Charles G. Sutherland, M.D.

ROENTGEN-RAY THERAPY

The Roentgen Therapy of Tuberculous Lymphadenitis and Orchiepididymitis. Bruno Faccini. Arch. di Radiol., September-October, 1934, **10,** 574–581.

From the excellent results obtained in these cases, Faccini is of the opinion that surgery should be abandoned for both of these diseases, and that the method of choice is roentgen therapy.

E. T. Leddy, M.D.

THE SPINE

Dislocations of the Cervical Spine: Some Predisposing Causes. Theodore P. Brookes. Jour. Am. Med. Assn., March 16, 1935, **104,** 902–905.

Reviewing a series of 65 cases of traumatic dislocations of the neck the author was impressed with the presence of systemic predisposing causes in a certain small group. As a toxic predisposition, alcoholism headed the list. Among destructive bone conditions, he classified tuberculosis and osteo-arthritis as direct causative factors and did not include them in the study of traumatic dislocations. Three cases developed in adults during treatment of other conditions. One he thought might be of non-traumatic origin, weakened soft tissues permitting dislocation with a minimum of violence. Two patients suffered rotary dislocation of the atlas during treatment by cultists. In five cases in children during the prodromal stage of an illness careful examination revealed that a dislocation of one of the vertebra had resulted from a fall.

Roentgenograms, accurately taken and carefully interpreted, will verify the clinical observations in a majority of instances. Routine roentgenograms call for three exposures: lateral of the cervical spine and two anteroposterior views, of which one is taken through the open mouth to show the first two vertebræ. Frequently, additional oblique views are required to show the articular processes.

Charles G. Sutherland, M.D.

THE STOMACH

Peroral Gastroscopy, Including Examination of the Supradiaphragmatic Stomach. Chevalier Jackson and Chevalier L. Jackson. Jour. Am. Med. Assn., Jan. 26, 1935, **104,** 269–274.

There are three methods of gastroscopy: one by using an open tube, another by using a lens system, and a third by combining both the open tube and the lens system. Each of these methods has its uses and limitations.

The open tube is of the method required for the removal of foreign bodies, and the taking of specimens of tissue for histologic examination. It has all the advantages of looking directly at tissues examined rather than at a lens-projected or prism-deflected image.

Lens system gastroscopy has the advantage that a much larger field of vision is available. The limitation is the danger of introduction of an instrument presenting no esophageal lumen ahead. This danger is obviated by the introduction of an open tube through which a lens system is passed.

Almost all the danger in gastroscopy is associated with the insertion through the esophagus, especially at the cricopharyngeal and diaphragmatic pinch-cocks. The watchword of safety is "find the lumen."

The contra-indications are few, and examination is indicated in every patient with gastric symptoms for diagnosis, unless there are over-balancing contra-indi-

cations. Hematemesis is a strong indication for gastroscopy; a tentative diagnosis of hysterical gastric neurosis is a clear indication for the same, as is an uncomplicated gastritis.

C. G. SUTHERLAND, M.D.

Roentgen Diagnosis of Carcinoma at the Cardia. William H. Stewart and H. Earl Illick. Am. Jour. Roentgenol. and Rad. Ther., July, 1934, **32,** 43–51.

Cancer of the cardia of the stomach comprises about one-sixth of the cancers involving this organ, and is not suspected unless dysphagia is present when it is already inoperable. The technic of the roentgen examination of the cardia, the roentgen signs, and the symptoms and differential diagnosis of cancer of this region are described. The roentgen signs listed are: any dilatation of the lower esophagus; any abnormal retention of barium in the lower esophagus; barium passing through the esophagus in a continuous stream; narrowed esophagus and unchanging canalization through tumor; frozen mass from infiltration of lower esophagus; mass visible in gas bubble or deformity of latter; distorted rugal pattern or visibility of mass by contracted lumen; barium forking over the mass; gastric hypermotility; esophageal antiperistalsis, and increase in the width of the space between the diaphragm and the fundus.

The authors deplore the examination of the stomach by physicians whose sole roentgen training is the mere possession of a machine. They urge roentgen examination when gastric symptoms are present.

S. M. ATKINS, M.D.

TUBERCULOSIS (PULMONARY)

From Pathology to Epidemiology in Tuberculosis: Softening of the Caseous Tubercle and its Results. Esmond R. Long. Jour. Am. Med. Assn., May 25, 1935, **104,** 1883–1888.

The problem of softening of the caseous tubercle may justly be considered the key problem in tuberculosis. If caseous tubercles did not soften, the disease would be self-limited and would die out with the end of the present cases, except for occasional cases dependent on unusual methods of transmission. The lung is infected by tubercle bacilli, cellular and subsequently caseous tubercles are formed and some of these soften. The softened caseous matter is discharged into the bronchioles and aspirated into other parts of the lung, with the production of new tubercles, some of which in turn soften; or it is coughed into the outside world, where other people may be infected. Associated with the softening, an extraordinary multiplication of tubercle bacilli occurs. At the stage when the product of tuberculous infiltration first discharges into a bronchus, it has its maximum infective power. Not before, nor again after, are tubercle bacilli to be found in the region concerned, in the concentration coincident with softening. Softening occurs quite as commonly in the absence of leukocytes as in their presence. The fundamental nature of the process of softening is still unknown. It is not equivalent to suppuration. Attempts to put it on an allergic basis have not been entirely successful.,

Successful treatment of tuberculosis by lung collapse owes its favorable outcome as much to prevention of drainage of liquefying tubercles as to the obliteration of large cavities. Lung collapse, improperly applied, particularly with excessive pressure, even when obvious cavities are obliterated, may result unfavorably through expulsion of highly infective liquefying matter into tributary bronchioles. The most appropriate lung collapse, as far as the softening tubercle is concerned, is that which stops motion of the lung and partially or completely obliterates the small bronchiolar outlets from the liquefying masses.

CHARLES G. SUTHERLAND, M.D.

The Declining Death Rate from Tuberculosis in Children: An Analysis of Tuberculosis Deaths in Minnesota from 1915 to 1932. Ruth E. Boynton. Jour. Am. Med. Assn., May 25, 1935, **104,** 1875–1878.

There is a great deal of interest both in this country and in foreign countries in the prevention of tuberculosis in infants by the use of the B C G vaccine. Proponents of this method of preventing tuberculosis feel that the immunity produced by B C G vaccine will reduce the incidence of the disease in infants and young children who are intimately exposed to tuberculosis, thus reducing the mortality rate in this age group.

In Minnesota, where B C G vaccination has not been tried, tuberculosis mortality rates in children are lower and have decreased at a more rapid rate than that reported by Wallgren in Gothenburg, Sweden, with the use of the B C G vaccine. The Minnesota rates are reviewed in a series of charts and tables.

The types of tuberculosis causing the greatest number of deaths in children in the order of their importance were tuberculous meningitis, pulmonary tuberculosis, and miliary tuberculosis. The largest number of deaths from tuberculous meningitis occurred in children under five years of age, and from pulmonary tuberculosis in those between 10 and 15 years of age. The highest mortality rate from both types was found in the group under one year of age. The greatest percentage of reduction in mortality in both types is in children under one year of age.

CHARLES G. SUTHERLAND, M.D.

Tuberculosis among Employees of the Minneapolis Schools. Francis E. Harrington, J. Arthur Myers, and Ida Levine. Jour. Am. Med. Assn., May 25, 1935, **104,** 1869–1874.

With a feeling that during the next five years nearly every physican in this country will be called on to take a part in actual examination of teachers and children for tuberculosis or will be consulted by parents and others concerning the advisability of, or information regarding, such examinations, these authors review their experiences in the survey of the Minneapolis schools.

Workers in other fields had found that children taught by teachers with open tuberculosis showed a much

higher incidence of positive tuberculin reactions than those taught by other teachers. Considerable preparation for such a survey was necessary; proper information had to be furnished various groups regarding its necessity. The procedure was the administration of tuberculin tests and the preparation of x-ray films of the positive tuberculin reactors, in addition to those who refused the tuberculin test. All manner of objections to the test had to be overcome. Reports on tuberculin test readings and reports on x-ray readings were made in writing to each individual concerned and forwarded under seal, making them strictly confidential. The highest reading was 82 per cent positive out of 23 persons tested, the lowest, 10 per cent positive out of ten teachers tested.

The chief advantages of such a survey are: First, disease may be detected before it has produced significant symptoms and while it can be treated successfully in a short time, thus saving the teacher a long period of inactivity from work. Such cases, by adequate treatment, may be prevented from breaking down so as to be a menace to the children and other teachers. Thus, the environment as far as tuberculosis is concerned becomes much safer from the standpoint both of the teacher and the child. Second, compulsory examinations often lead to investigation on the part of the teacher so that she becomes informed concerning the contagious nature of tuberculosis. Many such teachers become enthusiastic workers in the tuberculosis control program. This should lead ultimately to the enlistment and the support of great educational associations, which will be a valuable acquisition to the forces against tuberculosis.

CHARLES G. SUTHERLAND, M.D.

Interpretation of Roentgenograms in Pulmonary Tuberculosis. Henry K. Taylor. Jour. Am. Med. Assn., March 16, 1935, **104,** 898–900.

Serial roentgen studies of pathologic changes of superinfections and reinfections (secondary) in pulmonary tuberculosis reveal that lesions are either exudative or productive in character, from the earliest time that patients come under observation. These lesions have a tendency to heal. The end-result of the healing manifestations in pulmonary tuberculosis, demonstrable on the roentgen film, permits of a division into five types.

The exudative lesion terminates in one of three ways: (1) It may completely resolve and leave no traces in the roentgenogram; (2) it may resolve and leave a residual of a few fibrotic strands, or (3) it may undergo caseation and cavity formation. The productive lesions present themselves in one of two forms: (1) fibrotic strands, with small nodules, and (2) fibrosis, with numerous small cavitations resembling a bronchiectasis.

The roentgenographic study of the pathologic changes in tuberculosis reveals a qualitative as well as a quantitative component. The pathologic mutations observed in serial roentgenograms reveal whether a lesion is benign (running mild clinical course) or malignant (running a stormy course, metastasizing and spreading). The malignant are the types that compel the use of collapse therapy. This information aids in determining prognosis and treatment.

CHARLES G. SUTHERLAND, M.D.

TUMORS (DIAGNOSIS)

The Roentgen Diagnosis and Treatment of Tumors of the Bladder: Their Serial Study with Pneumocystograms, Showing Results of Treatment by Irradiation. George E. Pfahler and Jacob H. Vastine. Jour. Am. Med. Assn., Feb. 23, 1935, **104,** 609–612.

Pneumocystography is harmless and painless, and requires no great amount of paraphernalia. It can be used in conjunction with cystoscopy, or at times when cystoscopy cannot be performed. The technic is given in detail; also, the objections to the examination and the interpretation of the findings by this method are discussed. In the treatment of small benign tumors, the authors recommend preliminary irradiation, and cystoscopic electrocoagulation, followed by an additional moderate amount of irradiation.

In dealing with large and definitely malignant tumors, the family physician, the urologist, and the radiologist should co-operate in a general plan of treatment to obtain the best results.

The authors believe the treatment should be arranged with the purpose of overcoming the disease completely by irradiation. It may be necessary to destroy remaining tissue in some by electrocoagulation. As a result of irradiation, one commonly succeeds in arresting the hematuria, sometimes within a few days, but generally within a few weeks. In the more sensitive tumors, one may expect the entire tumor to disappear.

By means of the pneumocystogram, the progressive reduction in size of the tumor may be measured.

C. G. SUTHERLAND, M.D.

Blood Vessel Tumor of the Spinal Cord in a Boy Aged Nine Years, with Special Reference to a New Diagnostic Syndrome. William C. Black and Harold K. Faber. Jour. Am. Med. Assn., May 25, 1935, **104,** 1889–1891.

These authors found record of 63 cases of blood vessel tumors and varices of the spinal cord. Of this number, 10 per cent were purely arterial or presented an arterial component. The remaining 90 per cent were composed of about equal numbers of true neoplastic hemangiomas and of venous dilatations; the latter are not neoplastic formations but have been included in all reviews of the subject. Only one case of blood vascular cord tumor has been reported, prior to the one the authors present, in an individual under ten years of age. They report a case of intradural venous blood vascular tumor, probably hemangio-endothelioma with associated varices. The combination noted of the Froin syndrome, a negative Queckenstedt test becoming positive after with-

drawal of spinal fluid below the lesion, and a peculiar distribution of iodized oil in droplets, suggests that it may be pathognomonic of subarachnoid varices and vascular tumors of the cord large enough to obstruct the subarachnoid space.

CHARLES G. SUTHERLAND, M.D.

TUMORS (THERAPY)

A Classification of Tumors from the Standpoint of Radiosensitiveness. Arthur U. Desjardins. Am. Jour. Roentgenol. and Rad. Ther., October, 1934, **32,** 493–499.

The writer believes that the basic law of a specific range of sensitiveness of each variety of cells in the body, normal or pathologic, to roentgen rays or radium has not been as widely recognized and utilized as it should be. He emphasizes particularly the value of this basic law in the classification of various tumors, and states that in the future it is entirely possible that a more correct and satisfactory classification of given tumors will be accomplished by their reaction to radiation rather than by microscopic classification by pathologists. He recognizes full well that this specific range of sensitivity of different cells is not the sole factor determining the results of radiation therapy. It is dependent also upon blood supply and exposure to previous radiation, and there are, of course, variations in reaction of different individual cells of the same type because of these cells being in different stages of metabolism. The lymphocyte, the metabolic cycle of which among human cells is the shortest, is the most radiosensitive, while the nerve cell, the cycle of which is the longest, is the most resistant to radiation.

Classifying cells according to their radiosensitiveness from the most sensitive to the least sensitive, the writer offers the following classification: Lymphoid cells; polymorphonuclear and eosinophilic leukocytes; epithelial cells, comprising (1) mucus-secreting epithelial cells, (2) basal epithelium, (3) alveolar epithelium, and (4) epithelium of the tubules of the kidneys; endothelial cells of blood vessels, pleura, and peritoneum; connective tissue cells; muscle cells; bone cells; fat cells, and nerve cells. Thus, the epithelium of the skin stands about half-way between lymphocytes on the one hand and nerve cells on the other.

Neoplasms are divided into three main groups: (1) the radiosensitive tumors, the sensitiveness of which is greater than that of skin; (2) the moderately radiosensitive tumors, the gross sensitiveness of which approximates that of the skin, and (3) radioresistant tumors, the sensitiveness of which is less than that of skin.

Radiosensitiveness, rate of metabolism, and life cycle of cells appear to be closely interrelated.

In the radiosensitive group there are included the lymphoblastomas and lympho-epitheliomas, diffused endothelioma, embryonal carcinomas of the testis and ovary, giant-cell and multiple myeloma bone tumors, Wilms' tumor of the kidney, basal-cell and transitional epitheliomas, mucoid carcinomas of the intestinal tract, and hemangiomas.

In the moderately radiosensitive tumors are included the following: carcinoma of the uterine cervix; carcinoma (not adenocarcinoma) of the thyroid; epithelioma of the tonsil and pharynx, bronchus, lip, eyelids, mouth, tongue, and squamous type of skin; carcinoma of the breast and rectum, and chrondrosarcoma of the bone.

The radioresistant group includes the fibromas and fibrosarcomas, adenocarcinoma anywhere, except possibly in the cervix, carcinoma of the esophagus and stomach, hypernephroma, sarcoma of bone, melanoepithelioma, mixed tumor of parotid, teratoma, neurofibroma, chondroma, lipoma, myxoma, and myxosarcoma.

In general, the radiosensitiveness of metastases corresponds to that of the primary lesion, hence the diagnostic value of the therapeutic test may still be commonly applied to the secondary deposits when the primary tumor cannot be localized.

J. E. HABBE, M.D.

Bone Tumors and Irradiation. Louis C. Kress. Canadian Med. Assn. Jour., June, 1935, **32,** 651–654.

Kress evaluates irradiation in the treatment of bone tumors in a short systematic discussion of the various important types of bone pathology. The radiosensitiveness of each is briefly considered and in cases in which therapy is satisfactory a technic is outlined. Among the tumors considered are; giant-cell tumor, osteitis fibrosa cystica, Paget's disease, the various types of sarcoma and metastatic carcinoma.

W. A. SODEMAN, M.D.

Modified "Coutard" Roentgen Therapy. James M. Martin and Charles L. Martin. Jour. Am. Med. Assn., Feb. 23, 1935, **104,** 605–608.

Experienced radiologists discovered long ago that the actual cure of carcinoma requires the administration of from 5 to 10 erythema doses of x-rays, and even more in some instances. It has been their practice to use from 5 to 12 erythema doses as an effective treatment for squamous-cell carcinoma of the skin for more than ten years. They used the so-called "carcinoma dose" with the hope that the shorter wave lengths might possess some unknown properties that would compensate for the reduced dosage. Such did not prove to be the case in their experience.

High voltage therapy is used principally in treating tumors situated beneath normal structures, and investigators have made many attempts to increase the tumor dose without materially increasing the effect on the normal tissues; in other words, they have tried to increase the selective action of the rays. In America, this activity has been directed for the most part toward the production of huge tubes and machines operating at higher voltages and producing much shorter wave lengths. In Europe, investigators have been more interested in changes in intensity (roentgens per minute),

and in the time consumed in administering radiation. Results possessing greater promise have been obtainecl by this method.

The authors review the Coutard technic and point out that the chief objection to it is the amount of time involved in its administration. They describe in detail a modification of the Coutard technic in which an economy of time is brought about through a reduction in filter from 2 mm. of zinc to 0.75 mm. of copper. Contrary to the belief of many, this produces only a slight change in the wave length so long as the voltage remains the same. They have found this to be apparently efficient, and much less time-consuming than the French procedure.

C. G. SUTHERLAND, M.D.

THE UTERUS

Radiation Therapy in Cancer of the Cervix. William P. Healy. Canadian Med. Assn. Jour., June, 1935, **32**, 647–651.

As a guide in planning treatment of cancer of the cervix, Healy uses the following clinical classification: (1) Early cases—disease limited to the cervix; (2) Borderline cases—moderate parametrial involvement; (3) Advanced cases—extensive involvement of the parametria and vaginal vault; (4) Very advanced cases—"frozen" pelvis, with or without vesical or rectal fistula, in which only palliative treatment or nothing at all can be attempted.

Group 1 is favorable for cure, and from 50 to 60 per cent should show a five-year cure. Radium can be applied at once without risk to the lesion, followed by deep x-radiation. Groups 2 and 3 constitute from 75 to 80 per cent of all the patients. The cervical lesion is usually extensively ulcerated, infected, and necrotic. It is unwise to apply radium immediately without preliminary treatment. In 3,000 cases the best results with least risk to the patient were obtained by giving deep x-radiation first and withholding radium until definite improvement and response to x-ray was observed, as shown by shrinkage in size of the lesion, disappearance of soft necrotic tissue, and replacement with a healthy-appearing surface. Often the primary lesion showed complete surface healing before any radium was applied. Group 4, if treated at all, received deep x-radiation and occasionally small applications of radium.

The comparison of results with those of others showed little variation. This led Healy to an improved method of radiation for the parametrial metastases. The dosage of effective radiation was increased by reducing the amount given at each treatment, increasing the number of treatments and adding two fields, six in all. This technic increases considerably the amount of effective radiation distributed throughout the parametrium and it is hoped will inhibit metastasis. The series with the improved technic is not large enough to evaluate as yet.

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